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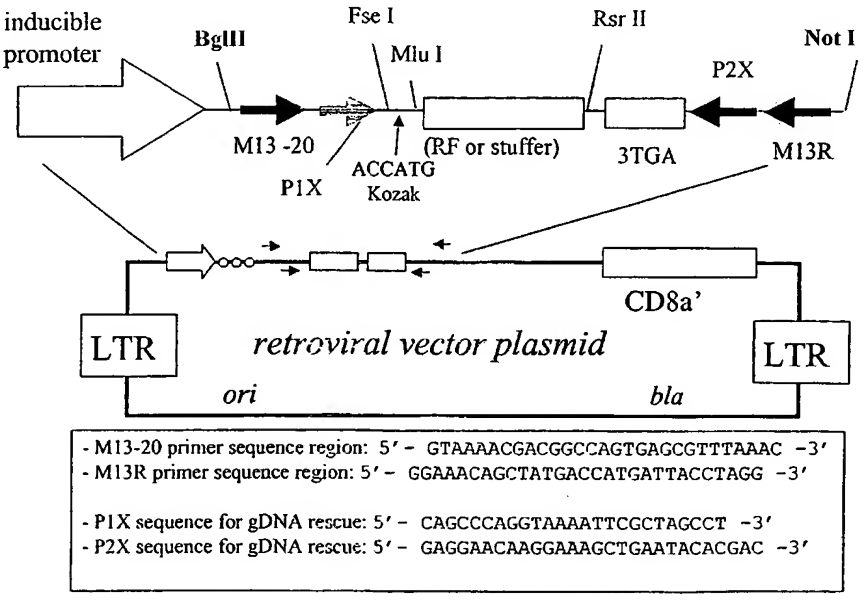
(54) Title: TARGETS FOR CONTROLLING CELLULAR GROWTH AND FOR DIAGNOSTIC METHODS




(57) Abstract: A method of identifying a compound that induces apoptosis is disclosed. The method includes identifying compounds that inhibit the expression and/or activity of a target. Also disclosed are methods for inducing apoptosis by inhibiting one of the targets. The invention further includes methods for the diagnosis of a tumor that include determining the level of at least one of the targets as a biomarker in a patient sample, the level of the biomarker being indicative of the presence of tumor cells.

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# TARGETS FOR CONTROLLING CELLULAR GROWTH AND FOR DIAGNOSTIC METHODS

## FIELD OF THE INVENTION

The present invention relates to methods for inducing apoptosis in cells by inhibiting targets involved in the suppression of apoptosis, and to identifying compounds useful in such methods. The present invention also relates to methods for the diagnosis of cancer in a patient using the targets identified by the present invention as biomarkers.

## BACKGROUND OF THE INVENTION

The p53 tumor suppressor protein is an essential component in the regulation of the cell cycle, senescence, and programmed cell death (apoptosis). This protein regulates transcription of many genes in response to DNA damage and various transforming stimuli. The functional inactivation of p53 can occur through the action of viral oncoproteins, or through over-expression of the hdm2 (human) or mdm2 (murine) oncogene protein. Additional tumor suppressors, such as the $p14^{ARF}$ product of the INK4a gene, regulate the functional activity of p53. In the case of $p14^{ARF}$, the suppressor interacts with hdm2 and thereby prevents the mentioned oncoprotein from inhibiting p53. An alternative translation product of the INK4a locus, p16INK4a, a cyclin-dependent kinase inhibitor, also contributes to normal growth control through its regulation of the Rb pathway.

When regulation of the cell cycle, senescence, and apoptosis is not functioning properly, uncontrolled cell growth and tumor formation occurs. Because of the complicated regulation of these cell functions, there are many potential points in a variety of regulatory pathways of a cell for intervention. By inhibiting the expression of genes important to cell growth and to suppression of apoptosis or the proteins encoded by them, it is possible to induce control cell growth and apoptosis in a cell, thereby preventing tumor formation. Once such genes or proteins are identified as targets, assays can be conducted for drug discovery to find inhibitors suitable for use as therapeutic agents. In addition, such genes or proteins are useful as markers of tumor formation.

There is an ongoing need to identify new targets and develop new assays for the identification of therapeutic compounds useful in the control of cell growth and tumor formation.

## SUMMARY OF THE INVENTION

This invention provides methods for identifying compounds that induce apoptosis by inhibiting target genes or gene products involved in the control of cell growth. The present invention also includes a method for inducing apoptosis in a cell by inhibiting such a target gene or gene product by, in one embodiment, contacting cells susceptible to uncontrolled growth with an inhibitory compound in an amount sufficient to inhibit said biochemical activity or expression. More particularly, targets of the present invention include any of the genes or gene products set forth in Table 1, which can also be identified as genes and gene products comprising SEQ ID NOs:1-80 (with odd numbered identifiers referring to nucleic acid sequences and even numbered identifiers referring to amino acid sequences).

In one embodiment, the present invention relates to a method of identifying a compound that induces apoptosis in a cell that includes contacting the cell with a putative apoptosis-inducing compound and determining whether the compound inhibits the expression and/or activity of a target selected from the group consisting of any of the targets listed in Table 1 (or comprising any of SEQ ID NOs:1-80). The target can have been validated as being involved in tumor cell growth, such as by a process of inhibiting the target in a cell by a method selected from gene knock-out, anti-sense oligonucleotide expression, use of RNAi molecules and GSE expression, or assaying the cell for the ability of the cell to grow. The cell can be a tumor cell line. The step of determining can be selected from assaying for reduced expression of the target and assaying for reduced activity of the target. The expression of the target can be measured by methods including, but not limited to, polymerase chain reaction or by using an antibody that specifically recognizes the target. The activity of the target can be measured by methods including, but not limited to, measuring the amount of a product generated in a biochemical reaction mediated by the target or by measuring the amount of a substrate consumed in a biochemical reaction mediated by the target. The inhibitor can be identified by methods including, but not limited to, determining the three-dimensional structure of the target or by determining the three-dimensional structure of an inhibitor by using computer software capable of modeling the interaction of the target and putative test compounds.

Another embodiment of the present invention is a method for inducing apoptosis in a cell by inhibiting a target selected from any of the genes or products encoded thereby

listed in Table 1 (also represented herein as genes or gene products comprising any of SEQ ID NOs:1-80).

A further embodiment of the present invention is a method for the diagnosis of a tumor that includes determining the level of a biomarker selected from any of the genes or products encoded thereby listed in Table 1 (also represented herein as genes or gene products comprising any of SEQ ID NOs:1-80) in a patient test sample. In this method, the level of the biomarker is indicative of the presence of tumor cells. The presence of the biomarker at an increased level as compared to a normal baseline control is an indication of the presence a tumor, a possible predisposition to such tumor or a susceptibility to an anti-cancer therapeutic treatment. The level of the biomarker can be determined by conventional methods such as expression assays to determine the level of expression of the gene, by biochemical assays to determine the level of the gene product, or by immunoassays. In one embodiment of this method, the level of the biomarker can be determined by identifying the biomarker as a cell surface molecule in tissue or by detecting the biomarker in soluble form in a bodily fluid, such as serum, that can be immobilized. The biomarker level can be determined by contacting a patient test sample with an antibody, or a fragment thereof, that binds specifically to the biomarker and determining whether the anti-biomarker antibody or fragment has bound to the biomarker. The biomarker level can be determined by using a first monoclonal antibody that binds specifically to the biomarker and a second antibody that binds to the first antibody. This method can be used to determine the prognosis for cancer in the patient or to determine the susceptibility of the patient to a therapeutic treatment.

## BRIEF DESCRIPTION OF THE DRAWINGS OF THE INVENTION

Fig. 1 illustrates a schematic of the features of theV98 vector.

Fig. 2 illustrates a schematic drawing of the construction of the V87 vector.

Fig. 3 illustrates a schematic drawing of the construction of the V98 vector

## DETAILED DESCRIPTION OF THE INVENTION

The present invention includes methods for identifying protective compounds that control cell growth and induce apoptosis by using genes that encode products that are necessary for protecting cells from apoptosis as targets in the design of therapeutic agents. The invention further includes compounds for use in the treatment or prevention of tumor

growth. Such compounds include chemical compounds and biological compounds. Chemical compounds or biological compounds include any chemical or biological compound that disrupts or inhibits one or more biological functions required for controlling cell growth. Preferred chemical compounds include small molecule inhibitor or substrate compounds, such as products of chemical combinatorial libraries. Preferred biological compounds include peptides, anti-sense molecules and antibodies.

The invention also includes methods for the diagnosis of cancer or for a prognosis of cancer or for determination of susceptibility to cancer treatments, by determining the level of expression of target genes and proteins of the present invention (also referred to as tumor antigens (TAGs)) in patient samples. The targets may originate from different parts of the cell and may be cell surface proteins, intracellular proteins or proteins that are secreted from the cell. There is a distinction between tissue, individual and species-specific cellular markers that may also be present physiologically as differentiation antigens on cells. There may be targets that are intermediate products released, over expressed or under expressed during the growth of a tumor cell type which can change upon further differentiation. The level of the target gene or protein can be determined by conventional methods such as expression assays to determine the level of expression of the gene, by biochemical assays to determine the level of the gene product, or by immunoassays. If appropriate, the marker can be identified as a cell surface molecule in tissue or in a bodily fluid, such as serum. These methods are described in detail below. The present invention provides much needed markers that permit an improved and more specific diagnosis of cancer, including the possible distinction between various tumor types, the prediction of tumor formation and the patient susceptibility to certain known cancer treatments.

The present invention is based, in part, on the present inventors' isolation of certain GSEs from human cells that prevent cell growth, and the discovery that such nucleic acid molecules correspond to fragments of certain genes. In that regard, any cellular phenotype or protein associated with cell growth can be used to select for such nucleic acid molecules or proteins encoded thereby.

More specifically, targets of the present invention have been identified as corresponding to genetic suppressor elements (GSEs) that control cell growth. The GSX™ System technology allows rapid screening for the inhibitors of gene function in the form of genetic suppressor elements. Briefly, a Genetic Suppressor Element (GSE), is

a gene fragment, which, when expressed in cells, acts as a genetic inhibitor of the corresponding intact gene in those cells. A GSE can exert its effect through either an antisense, or a dominant negative peptide mechanism. GSEs are selected from libraries of DNA fragments, generated by random breakage of sets of test genes, cloned in a retroviral or other expression vector. The RFL clones are introduced into a population of test cells at approximately one test fragment per cell. Cells with a desired new phenotype, resulting from the expression of a GSE, are isolated on the basis of any selectable parameter. The GSEs are recovered from the selected cells and characterized by DNA sequence analysis and further functional assays.

GSEs having the ability to control cell growth can be functional in the sense orientation (and encode a peptide thereby), and can be functional in the antisense orientation (and encode antisense RNAs thereby). These GSEs are believed to down-regulate the corresponding gene from which they were derived by different mechanisms. Such a corresponding gene is referred to herein as a "target gene" and its product (*i.e.*, protein encoded by the coding region of the gene) is referred to as a "target product" or "target protein". As used herein, the term "target" alone can refer collectively to a target gene and its corresponding target product, or to useful portions thereof. Sense-oriented GSEs exert their effects as transdominant mutants or RNA decoys. Transdominant mutants are expressed proteins or peptides that competitively inhibit the normal function of a wild-type protein in a dominant fashion. RNA decoys are protein binding sites that titrate out these wild-type proteins. Anti-sense oriented GSEs exert their effects as antisense RNA molecules, *i.e.*, nucleic acid molecules complementary to the mRNA of the target gene. These nucleic acid molecules bind to mRNA and block the translation of the mRNA. In addition, some antisense nucleic acid molecules can act directly at the DNA level to inhibit transcription.

Specific targets of the present invention are shown below in the Examples section in Table 1. The targets include the genes and products of the genes or any useful portion thereof. Methods of the present invention for identifying therapeutic compounds by identifying an inhibitor of a target include identifying an inhibitor of: a target gene from Table 1, as well as target products encoded by any of the foregoing. Diagnostic methods for detecting cancer in a patient include detection of a target gene from Table 1, as well as target products encoded by any of the foregoing, and useful portions thereof. More specifically, the targets of the present invention include genes comprising all or a portion

of any of the nucleic acid sequences represented by SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, or 79. These nucleic acid molecules encode the following target proteins, respectively: angio-associated, migratory cell protein (AAMP; SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8; SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17; SEQ ID NO:6), adenylate cyclase 3 (ADCY3; SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1; SEQ ID NO:10), bladder cancer associated protein (BLCAP; SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5; SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81; SEQ ID NO:16), CD9 antigen (p24) (CD9; SEQ ID NO:18), claudin 4 (CLDN4; SEQ ID NO:20), chloride intracellular channel 1 (CLIC1; SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2; SEQ ID NO:24), CTL2 (CTL2; SEQ ID NO:26), endothelin converting enzyme 1 (ECE1; SEQ ID NO:28), ephrin-B1 (EFNB1; SEQ ID NO:30), flotillin 2 (FLOT2; SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3; SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS; SEQ ID NO:36), jagged 2 (JAG2; SEQ ID NO:38), junctional adhesion molecule 1 (JAM1; SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP; SEQ ID NO:42), similar to possible G-protein receptor (LOC146330; SEQ ID NO:44), CGI-78 protein (LOC51107; SEQ ID NO:46), lipoprotein lipase (LPL; SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5; SEQ ID NO:50), Lutheran blood group (Auberger b antigen included) (LU; SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1; SEQ ID NO:54), serum constituent protein (MSE55; SEQ ID NO:56), neuropathy target esterase (NTE; SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1; SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 3 (PPFIA3; SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4; SEQ ID NO:64), solute carrier family 16 (moncarboxylic acid transporters) member 3 (SLC16A3; SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5; SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1; SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2; SEQ ID NO:72), stanniocalcin 2 (STC2; SEQ ID NO:74), tumor

necrosis receptor superfamily member 21 (TNFRSF21; SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1; SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4; SEQ ID NO:80). In any of the assays described herein, one can use a full-length gene, including a regulatory region of the gene, or a nucleic acid molecule encoding the gene product (protein encoded by the gene) or any fragment of such nucleic acid molecules, or any gene product or fragment thereof that is suitable for use in an assay to identify inhibitors of the target for the purpose of regulating apoptosis or inhibition of tumor growth, or to detect cancer in a patient sample.

In one embodiment of the invention, the down-regulation of the concentration or activity of a target gene or product by an inhibitor (including a GSE) depletes a cellular component required for protecting cells from apoptosis resulting in control of cell growth. In another embodiment of the invention, the down-regulation of the concentration or activity of one target gene or product by an inhibitor (including a GSE) depletes a cellular component that interacts with another gene or gene product required for protecting cells from apoptosis resulting in control of cell growth. In a preferred embodiment of the invention, the two genes are members of the same biological pathway and one gene or gene product regulates the expression or activity of the other gene or gene product. In another preferred embodiment of the invention, the two genes are members of the same biological pathway and the substrate of a protein encoded by one gene is a product of a biochemical reaction mediated by the protein encoded by the other gene. In still another preferred embodiment of the invention, the two genes are members of the same biological pathway and the product of a protein encoded by one gene is a substrate of a biochemical reaction mediated by the protein encoded by the other gene. In another embodiment, the two genes encode proteins that are isozymes of each other. In a preferred embodiment, at least one of the genes encodes an enzyme.

Target genes or proteins identified using GSEs can be further evaluated using a variety of methods to validate their involvement in cell growth, suppression of apoptosis and tumor formation. Such methods include methods that disrupt or "knock out" the expression of a target gene in a cell capable of apoptosis. Knock-out methods include somatic cell knock-outs and inhibitory RNA molecules including anti-sense oligonucleotides, siRNA molecules, RNAi molecules and RNA decoys. Target genes or proteins can also be evaluated by methods that include nucleic acid-based experiments such as Northern Blots, Real Time polymerase chain reaction or high density microarrays.

Further evaluation can also be achieved using human/mouse xenograft models. For example, human tumor cells can be transfected with a GSE such that the GSE is expressed. Preferred tumor cells include HCT15, HT29, HCT116, SW480 and SW620 and MDA-MB-231 (*e.g.*, *see* Examples). The transfected cells can then be implanted into mice, preferably nude mice. The growth of the tumor cells in the mouse can then be measured.

Once a gene has been identified as a potential target for supporting cell growth, assays can be used for associating a potential target with different tumor types. These assays include determining gene and protein expression of potential targets in different tumor cell types at different points of differentiation. Another assay can include determining the presence of a potential marker in patient samples using standard protein detection methods known to those of skill in the art. Targets that have been associated with cancer are also referred to as biomarkers. Preferred biomarkers of the present invention are listed in Table 1 (*see* Examples section).

Once one or more members of a biological pathway are identified as required for cell growth, the present invention can include identifying additional members of a biological pathway that are also required for cell growth. Such subsequent identification is within the skill of one in the art. GSEs, and therefore preferred targets of the present invention, are identified by selecting cells that exhibit certain hallmarks of apoptosis upon expression of the GSEs. Isolated GSEs are further prioritized based on their specificity for a neoplastic transformation state, such as their activity in transformed and non-transformed cells, and based on the p53 pathway status in cells expressing the GSEs. For example, GSEs can be prioritized by determining if the GSEs have activity in a p53 dependent and/or independent manner. GSEs specific for the neoplastic transformation state are preferred for identifying targets for anti-cancer drugs.

It will be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, constructs, or reagents described herein, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the invention that will be limited only by the appended claims. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

As used herein, the term "isolated nucleic acid molecule" refers to a nucleic acid molecule that has been removed from its natural milieu (*i.e.*, a molecule that has been subject to human manipulation) and can include DNA, RNA, or derivatives of either DNA or RNA. An isolated nucleic acid molecule can be isolated from its natural source or can be produced using recombinant DNA technology (*e.g.*, polymerase chain reaction amplification) or chemical synthesis. Isolated nucleic acid molecules include natural nucleic acid molecules and homologs thereof, including, but not limited to, natural allelic variants and modified nucleic acid molecules in which nucleotides have been inserted, deleted, substituted, or inverted in such a manner that such modifications do not substantially interfere with the nucleic acid molecule's ability to control cell growth or encode a protein that controls cell growth.

It should also be appreciated that reference to an isolated nucleic acid molecule does not necessarily reflect the extent of purity of the nucleic acid molecule. Nucleic acid molecules can be isolated and obtained in substantial purity, generally as other than an intact chromosome. Usually, the nucleic acid molecule will be obtained substantially free of other nucleic acid sequences, generally being at least about 50%, and usually at least about 90% pure. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably.

According to the invention, reference to an "isolated nucleic acid molecule" refers to a nucleic acid molecule that is the size of or is smaller than a gene. Thus, an isolated nucleic acid molecule does not encompass isolated total genomic DNA or an isolated chromosome. As used herein, the term "gene" has the meaning that is well known in the art, that is, a nucleic acid sequence that includes the translated sequences that code for a protein ("exons") and the untranslated intervening sequences ("introns"), and any regulatory elements necessary to transcribe and/or translate the protein. Included in the invention are nucleic acid molecules that are less than a full-length gene or less than a full-length coding sequence, such as fragments of a gene or coding sequence comprising, consisting essentially of, or consisting of, for example, a fragment of any of the nucleic acid sequences for target genes described in the present invention. A coding sequence can include genomic DNA without introns, cDNA or RNA that encodes a protein. An isolated nucleic acid molecule can also include a specified nucleic acid sequence flanked

by (*i.e.*, at the 5' and/or the 3' end of the sequence) additional nucleic acids that do not normally flank the specified nucleic acid sequence in nature (*i.e.*, are heterologous sequences).

In one embodiment, an isolated nucleic acid molecule useful in a method of the present invention is produced using recombinant DNA technology (*e.g.*, polymerase chain reaction (PCR) amplification, cloning) or chemical synthesis. A nucleic acid molecule homologue can be produced using a number of methods known to those skilled in the art (see, for example, Sambrook et al., *ibid.*). For example, nucleic acid molecules can be modified using a variety of techniques including, but not limited to, classical mutagenesis techniques and recombinant DNA techniques, such as site-directed mutagenesis, chemical treatment of a nucleic acid molecule to induce mutations, restriction enzyme cleavage of a nucleic acid fragment, ligation of nucleic acid fragments, PCR amplification and/or mutagenesis of selected regions of a nucleic acid sequence, synthesis of oligonucleotide mixtures and ligation of mixture groups to "build" a mixture of nucleic acid molecules and combinations thereof. Nucleic acid molecule homologues can be selected from a mixture of modified nucleic acids by screening for the function of the protein encoded by the nucleic acid and/or by hybridization with a wild-type gene.

The term isolated nucleic acid molecule does not necessarily connote any specific minimum length unless set forth by reference to a minimum number of nucleotides or by a function of the nucleic acid molecule. The minimum size of a nucleic acid molecule of the present invention is generally a size sufficient to encode a protein having the desired biological activity, a size sufficient to inhibit the expression and/or activity of a target as described herein (*e.g.*, as in a GSE), a size sufficient for use in a screening assay or diagnostic method of the invention, or a size sufficient to form a probe or oligonucleotide primer that is capable of forming a stable hybrid with the complementary sequence of a nucleic acid molecule. As such, the size of a nucleic acid molecule of the present invention can be dependent on nucleic acid composition and percent homology or identity between the nucleic acid molecule and complementary sequence as well as upon hybridization conditions *per se* (*e.g.*, temperature, salt concentration, and formamide concentration) and the intended use of the nucleic acid molecule. The minimal size of a nucleic acid molecule that is used as an oligonucleotide primer or as a probe is typically at least about 12 to about 15 nucleotides in length if the nucleic acid molecules are GC-rich and at least about 15 to about 18 bases in length if they are AT-rich. There is no

limit, other than a practical limit, on the maximal size of a nucleic acid molecule of the present invention, in that the nucleic acid molecule can include a fragment of a gene, a portion of a protein encoding sequence, or a nucleic acid sequence encoding a full-length protein (including a complete gene).

Some embodiments of the present invention may include the production and/or use of a recombinant nucleic acid molecule comprising a recombinant vector and a nucleic acid molecule comprising a nucleic acid sequence encoding a gene or fragment thereof as described herein. According to the present invention, a recombinant vector is an engineered (*i.e.*, artificially produced) nucleic acid molecule that is used as a tool for manipulating a nucleic acid sequence of choice and for introducing such a nucleic acid sequence into a host cell. The recombinant vector is therefore suitable for use in cloning, sequencing, and/or otherwise manipulating the nucleic acid sequence of choice, such as by expressing and/or delivering the nucleic acid sequence of choice into a host cell to form a recombinant cell. Such a vector typically contains heterologous nucleic acid sequences, that is nucleic acid sequences that are not naturally found adjacent to nucleic acid sequence to be cloned or delivered, although the vector can also contain regulatory nucleic acid sequences (*e.g.*, promoters, untranslated regions) which are naturally found adjacent to nucleic acid molecules of the present invention or which are useful for expression of the nucleic acid molecules of the present invention (discussed in detail below). The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and typically is a plasmid. The vector can be maintained as an extrachromosomal element (*e.g.*, a plasmid) or it can be integrated into the chromosome of a recombinant organism (*e.g.*, a microbe or a plant). The entire vector can remain in place within a host cell, or under certain conditions, the plasmid DNA can be deleted, leaving behind the nucleic acid molecule of the present invention. The integrated nucleic acid molecule can be under chromosomal promoter control, under native or plasmid promoter control, or under a combination of several promoter controls. Single or multiple copies of the nucleic acid molecule can be integrated into the chromosome. A recombinant vector of the present invention can contain at least one selectable marker.

In one embodiment, a recombinant vector used in a recombinant nucleic acid molecule of the present invention is an expression vector. As used herein, the phrase "expression vector" is used to refer to a vector that is suitable for production of an encoded product (*e.g.*, a protein of interest). In this embodiment, a nucleic acid sequence

encoding the product to be produced is inserted into the recombinant vector to produce a recombinant nucleic acid molecule. The nucleic acid sequence encoding the protein to be produced is inserted into the vector in a manner that operatively links the nucleic acid sequence to regulatory sequences in the vector that enable the transcription and translation of the nucleic acid sequence within the recombinant host cell.

In another embodiment, a recombinant vector used in a recombinant nucleic acid molecule of the present invention is a targeting vector. As used herein, the phrase "targeting vector" is used to refer to a vector that is used to deliver a particular nucleic acid molecule into a recombinant host cell, wherein the nucleic acid molecule is used to delete or inactivate an endogenous gene within the host cell or microorganism (*i.e.*, used for targeted gene disruption or knock-out technology). Such a vector may also be known in the art as a "knock-out" vector. In one aspect of this embodiment, a portion of the vector, but more typically, the nucleic acid molecule inserted into the vector (*i.e.*, the insert), has a nucleic acid sequence that is homologous to a nucleic acid sequence of a target gene in the host cell (*i.e.*, a gene which is targeted to be deleted or inactivated). The nucleic acid sequence of the vector insert is designed to bind to the target gene such that the target gene and the insert undergo homologous recombination, whereby the endogenous target gene is deleted, inactivated or attenuated (*i.e.*, by at least a portion of the endogenous target gene being mutated or deleted).

Typically, a recombinant nucleic acid molecule includes at least one nucleic acid molecule of the present invention operatively linked to one or more expression control sequences, including transcription control sequences and translation control sequences. As used herein, the phrase "recombinant molecule" or "recombinant nucleic acid molecule" primarily refers to a nucleic acid molecule or nucleic acid sequence operatively linked to an expression control sequence, but can be used interchangeably with the phrase "nucleic acid molecule", when such nucleic acid molecule is a recombinant molecule as discussed herein. According to the present invention, the phrase "operatively linked" refers to linking a nucleic acid molecule to an expression control sequence (*e.g.*, a transcription control sequence and/or a translation control sequence) in a manner such that the molecule is able to be expressed when transfected (*i.e.*, transformed, transduced, transfected, conjugated or conduced) into a host cell. Transcription control sequences are sequences that control the initiation, elongation, or termination of transcription. Particularly important transcription control sequences are those that control transcription

initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in a host cell or organism into which the recombinant nucleic acid molecule is to be introduced.

According to the present invention, the term "transfection" is used to refer to any method by which an exogenous nucleic acid molecule (*i.e.*, a recombinant nucleic acid molecule) can be inserted into a cell. The term "transformation" can be used interchangeably with the term "transfection" when such term is used to refer to the introduction of nucleic acid molecules into microbial cells. In microbial systems, the term "transformation" is used to describe an inherited change due to the acquisition of exogenous nucleic acids by the microorganism and is essentially synonymous with the term "transfection." However, in animal cells, transformation has acquired a second meaning that can refer to changes in the growth properties of cells in culture (described above) after they become cancerous, for example. Therefore, to avoid confusion, the term "transfection" is preferably used with regard to the introduction of exogenous nucleic acids into animal cells, including human cells, and is used herein to generally encompass transfection of animal cells and transformation of microbial cells, to the extent that the terms pertain to the introduction of exogenous nucleic acids into a cell. Therefore, transfection techniques include, but are not limited to, transformation, chemical treatment of cells, particle bombardment, electroporation, microinjection, lipofection, adsorption, infection and protoplast fusion.

A recombinant cell is preferably produced by transforming a host cell with one or more recombinant molecules, each comprising one or more nucleic acid molecules operatively linked to an expression vector containing one or more expression control sequences.

"Hybridization" has the meaning that is well known in the art, that is, the formation of a duplex structure by two single-stranded nucleic acids due to complementary base pairing. Hybridization can occur between exactly complementary nucleic acid strands or between nucleic acid strands that contain some regions of mismatch. As used herein, reference to hybridization conditions refers to standard hybridization conditions under which nucleic acid molecules are used to identify similar nucleic acid molecules. Such standard conditions are disclosed, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs

Press, 1989. Sambrook et al., *ibid.*, is incorporated by reference herein in its entirety (*see* specifically, pages 9.31-9.62). In addition, formulae to calculate the appropriate hybridization and wash conditions to achieve hybridization permitting varying degrees of mismatch of nucleotides are disclosed, for example, in Meinkoth et al., 1984, *Anal. Biochem.* 138, 267-284; Meinkoth et al., *ibid.*, is incorporated by reference herein in its entirety. "Stringent hybridization" has a meaning well-established in the art, that is, hybridization performed at a salt concentration of no more than 1M and a temperature of at least 25 degrees Celsius. For example, conditions of 5X SSPE (750 mM NaCl, 50 mM Sodium Phosphate, 5 mM EDTA, pH 7.4) and a temperature of 55 degrees to 60 degrees Celsius are suitable. For example, in one embodiment, "moderately stringent conditions" can be defined as hybridizations carried out as described above, followed by washing in 0.2X SSC and 0.1% SDS at 42 degrees Celsius (Ausubel *et al.*, 1989, *Current Protocols for Molecular Biology, ibid.*).

More particularly, moderate stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 70% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (*i.e.*, conditions permitting about 30% or less mismatch of nucleotides). High stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 80% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (*i.e.*, conditions permitting about 20% or less mismatch of nucleotides). Very high stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 90% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (*i.e.*, conditions permitting about 10% or less mismatch of nucleotides). As discussed above, one of skill in the art can use the formulae in Meinkoth et al., *ibid.* to calculate the appropriate hybridization and wash conditions to achieve these particular levels of nucleotide mismatch. Such conditions will vary, depending on whether DNA:RNA or DNA:DNA hybrids are being formed. Calculated melting temperatures for DNA:DNA hybrids are 10°C less than for DNA:RNA hybrids. In particular embodiments, stringent hybridization conditions for DNA:DNA hybrids include hybridization at an ionic strength of 6X SSC (0.9 M $Na^+$) at a temperature of between about 20°C and about 35°C (low stringency), more preferably,

between about 28°C and about 42°C (more stringent), and even more preferably, between about 35°C and about 45°C (even more stringent), with appropriate wash conditions. In particular embodiments, stringent hybridization conditions for DNA:RNA hybrids include hybridization at an ionic strength of 6X SSC (0.9 M $Na^+$) at a temperature of between about 30°C and about 45°C, more preferably, between about 38°C and about 50°C, and even more preferably, between about 45°C and about 55°C, with similarly stringent wash conditions. These values are based on calculations of a melting temperature for molecules larger than about 100 nucleotides, 0% formamide and a G + C content of about 40%. Alternatively, $T_m$ can be calculated empirically as set forth in Sambrook et al., *supra*, pages 9.31 to 9.62. In general, the wash conditions should be as stringent as possible, and should be appropriate for the chosen hybridization conditions. For example, hybridization conditions can include a combination of salt and temperature conditions that are approximately 20-25°C below the calculated $T_m$ of a particular hybrid, and wash conditions typically include a combination of salt and temperature conditions that are approximately 12-20°C below the calculated $T_m$ of the particular hybrid. One example of hybridization conditions suitable for use with DNA:DNA hybrids includes a 2-24 hour hybridization in 6X SSC (50% formamide) at about 42°C, followed by washing steps that include one or more washes at room temperature in about 2X SSC, followed by additional washes at higher temperatures and lower ionic strength (*e.g.*, at least one wash as about 37°C in about 0.1X-0.5X SSC, followed by at least one wash at about 68°C in about 0.1X-0.5X SSC).

In one embodiment of the present invention, any amino acid sequence described herein can be produced with from at least one, and up to about 20, additional heterologous amino acids flanking each of the C- and/or N-terminal ends of the specified amino acid sequence. The resulting protein or polypeptide can be referred to as "consisting essentially of" the specified amino acid sequence. According to the present invention, the heterologous amino acids are a sequence of amino acids that are not naturally found (*i.e.*, not found in nature, *in vivo*) flanking the specified amino acid sequence, or that are not related to the function of the specified amino acid sequence, or that would not be encoded by the nucleotides that flank the naturally occurring nucleic acid sequence encoding the specified amino acid sequence as it occurs in the gene, if such nucleotides in the naturally occurring sequence were translated using standard codon

usage for the organism from which the given amino acid sequence is derived. Similarly, the phrase "consisting essentially of", when used with reference to a nucleic acid sequence herein, refers to a nucleic acid sequence encoding a specified amino acid sequence that can be flanked by from at least one, and up to as many as about 60, additional heterologous nucleotides at each of the 5' and/or the 3' end of the nucleic acid sequence encoding the specified amino acid sequence. The heterologous nucleotides are not naturally found (*i.e.*, not found in nature, *in vivo*) flanking the nucleic acid sequence encoding the specified amino acid sequence as it occurs in the natural gene or do not encode a protein that imparts any additional function to the protein or changes the function of the protein having the specified amino acid sequence.

As discussed above, one embodiment of the present invention relates to methods for identifying compounds that induce or increase or upregulate apoptosis in a cell by inhibiting genes or gene products involved in the control of cell growth. Once a gene has been identified as a target for supporting cell growth, an assay can be used for screening and selecting a chemical compound or a biological compound having activity as an anti-tumor therapeutic based on the ability of the compound to down-regulate expression of the gene or inhibit activity of its gene product. Reference herein to inhibiting a target, can refer to one or both of inhibiting expression of a target gene and inhibiting the translation and/or activity of its corresponding expression product. Such a compound can be referred to herein as therapeutic compound. For example, a cell line that naturally expresses the gene of interest or has been transfected with the gene or other recombinant nucleic acid molecule encoding the protein of interest is incubated with various compounds, also referred to as candidate compounds, test compounds, or putative regulatory compounds. A reduction of the expression of the gene of interest or an inhibition of the activities of its encoded product (*e.g.*, biological activity, which can include the involvement of the protein in the protection of the cell from apoptotic processes) may be used to identify a therapeutic compound. Therapeutic compounds identified in this manner can then be re-tested, if desired, in other assays to confirm their activities against cellular apoptotic processes.

In general, the biological activity or biological action of a protein refers to any function(s) exhibited or performed by the protein that is ascribed to the naturally occurring form of the protein as measured or observed *in vivo* (*i.e.*, in the natural physiological environment of the protein) or *in vitro* (*i.e.*, under laboratory conditions).

Modifications, activities or interactions which result in a decrease in protein expression or a decrease in the activity of the protein, can be referred to as inactivation (complete or partial), down-regulation, reduced action, or decreased action or activity of a protein. Similarly, modifications, activities or interactions which result in an increase in protein expression or an increase in the activity of the protein, can be referred to as amplification, overproduction, activation, enhancement, up-regulation or increased action of a protein. The biological activity of a protein according to the invention can be measured or evaluated using any assay for the biological activity of the protein as known in the art. Such assays can include, but are not limited to, binding assays, assays to determine internalization of the protein and/or associated proteins, enzyme assays, cell signal transduction assays (*e.g.*, phosphorylation assays), and/or assays for determining downstream cellular events that result from activation or binding of the cell surface protein (*e.g.*, expression of downstream genes, production of various biological mediators, etc.). The assay can also measure the ability of the protein to contribute to the regulation of apoptosis in a cell. Such assays are described in detail herein. According to the present invention, a biologically active fragment or homologue of a gene or protein maintains the ability to be useful in a method of the present invention. Therefore, the biologically active fragment or homologue maintains the ability to be used to identify regulators (*e.g.*, inhibitors) of the native gene or protein when, for example, the biologically active fragment or homologue is expressed by a cell. Therefore, the biologically active fragment or homologue has a structure that is sufficiently similar to the structure of the native gene or protein that a regulatory compound can be identified by its ability to bind to and/or regulate the expression or activity of the fragment or homologue in a manner consistent with the regulation of the native gene or protein.

Compounds to be screened in the methods of the invention include known organic compounds such as antibodies, products of peptide libraries, and products of chemical combinatorial libraries. Compounds may also be identified using rational drug design relying on the structure of the product of a gene. Such methods are known to those of skill in the art and involve the use of three-dimensional imaging software programs. For example, various methods of drug design, useful to design or select mimetics or other therapeutic compounds useful in the present invention are disclosed in Maulik et al., 1997, *Molecular Biotechnology: Therapeutic Applications and Strategies*, Wiley-Liss, Inc., which is incorporated herein by reference in its entirety.

As used herein, a mimetic refers to any peptide or non-peptide compound that is able to mimic the biological action of a naturally occurring peptide, often because the mimetic has a basic structure that mimics the basic structure of the naturally occurring peptide and/or has the salient biological properties of the naturally occurring peptide. Mimetics can include, but are not limited to: peptides that have substantial modifications from the prototype such as no side chain similarity with the naturally occurring peptide (such modifications, for example, may decrease its susceptibility to degradation); anti-idiotypic and/or catalytic antibodies, or fragments thereof; non-proteinaceous portions of an isolated protein (*e.g.*, carbohydrate structures); or synthetic or natural organic molecules, including nucleic acids and drugs identified through combinatorial chemistry, for example. Such mimetics can be designed, selected and/or otherwise identified using a variety of methods known in the art.

A mimetic can be obtained, for example, from molecular diversity strategies (a combination of related strategies allowing the rapid construction of large, chemically diverse molecule libraries), libraries of natural or synthetic compounds, in particular from chemical or combinatorial libraries (*i.e.*, libraries of compounds that differ in sequence or size but that have the similar building blocks) or by rational, directed or random drug design. *See* for example, Maulik et al., *supra*.

In a molecular diversity strategy, large compound libraries are synthesized, for example, from peptides, oligonucleotides, carbohydrates and/or synthetic organic molecules, using biological, enzymatic and/or chemical approaches. The critical parameters in developing a molecular diversity strategy include subunit diversity, molecular size, and library diversity. The general goal of screening such libraries is to utilize sequential application of combinatorial selection to obtain high-affinity ligands for a desired target, and then to optimize the lead molecules by either random or directed design strategies. Methods of molecular diversity are described in detail in Maulik, et al., *ibid.*

Maulik et al. also disclose, for example, methods of directed design, in which the user directs the process of creating novel molecules from a fragment library of appropriately selected fragments; random design, in which the user uses a genetic or other algorithm to randomly mutate fragments and their combinations while simultaneously applying a selection criterion to evaluate the fitness of candidate ligands; and a grid-based approach in which the user calculates the interaction energy between three dimensional

receptor structures and small fragment probes, followed by linking together of favorable probe sites.

As used herein, the term "test compound", "putative inhibitory compound" or "putative regulatory compound" refers to compounds having an unknown or previously unappreciated regulatory activity in a particular process. As such, the term "identify" with regard to methods to identify compounds is intended to include all compounds, the usefulness of which as a regulatory compound for the purposes of inhibiting cell growth is determined by a method of the present invention.

In one embodiment of the invention, inhibitors of cell growth are identified by exposing a target gene to a test compound; measuring the expression of a target; and selecting a compound that down-regulates (reduces, decreases, inhibits, blocks) the expression of the target. For example, the putative inhibitor can be exposed to a cell that expresses the target gene (endogenously or recombinantly). A preferred cell to use in an assay includes a mammalian cell that either naturally expresses the target gene or has been transformed with a recombinant form of the target gene, such as a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding the target protein or a useful fragment thereof. Methods to determine expression levels of a gene are well known in the art.

The conditions under which a cell, cell lysate, nucleic acid molecule or protein of the present invention is exposed to or contacted with a putative regulatory compound, such as by mixing, are any suitable culture or assay conditions. In the case of a cell-based assay, the conditions include an effective medium in which the cell can be cultured or in which the cell lysate can be evaluated in the presence and absence of a putative regulatory compound. Cells of the present invention can be cultured in a variety of containers including, but not limited to, tissue culture flasks, test tubes, microtiter dishes, and petri plates. Culturing is carried out at a temperature, pH and carbon dioxide content appropriate for the cell. Such culturing conditions are also within the skill in the art. Cells are contacted with a putative regulatory compound under conditions which take into account the number of cells per container contacted, the concentration of putative regulatory compound(s) administered to a cell, the incubation time of the putative regulatory compound with the cell, and the concentration of compound administered to a cell. Determination of effective protocols can be accomplished by those skilled in the art based on variables such as the size of the container, the volume of liquid in the container,

conditions known to be suitable for the culture of the particular cell type used in the assay, and the chemical composition of the putative regulatory compound (*i.e.*, size, charge etc.) being tested. A preferred amount of putative regulatory compound(s) can comprise between about 1 nM to about 10 mM of putative regulatory compound(s) per well of a 96-well plate.

As used herein, the term "expression", when used in connection with detecting the expression of a target of the present invention, can refer to detecting transcription of the target gene and/or to detecting translation of the target protein encoded by the target gene. To detect expression of a target refers to the act of actively determining whether a target is expressed or not. This can include determining whether the target expression is upregulated as compared to a control, downregulated as compared to a control, or unchanged as compared to a control. Therefore, the step of detecting expression does not require that expression of the target actually is upregulated or downregulated, but rather, can also include detecting that the expression of the target has not changed (*i.e.*, detecting no expression of the target or no change in expression of the target). Expression of transcripts and/or proteins is measured by any of a variety of known methods in the art. For RNA expression, methods include but are not limited to: extraction of cellular mRNA and Northern blotting using labeled probes that hybridize to transcripts encoding all or part of one or more of the genes of this invention; amplification of mRNA expressed from one or more of the genes of this invention using gene-specific primers, polymerase chain reaction (PCR), and reverse transcriptase-polymerase chain reaction (RT-PCR), followed by quantitative detection of the product by any of a variety of means; extraction of total RNA from the cells, which is then labeled and used to probe cDNAs or oligonucleotides encoding all or part of the genes of this invention, arrayed on any of a variety of surfaces; *in situ* hybridization; and detection of a reporter gene. The term "quantifying" or "quantitating" when used in the context of quantifying transcription levels of a gene can refer to absolute or to relative quantification. Absolute quantification may be accomplished by inclusion of known concentration(s) of one or more target nucleic acids and referencing the hybridization intensity of unknowns with the known target nucleic acids (*e.g.* through generation of a standard curve). Alternatively, relative quantification can be accomplished by comparison of hybridization signals between two or more genes, or between two or more treatments to quantify the changes in hybridization intensity and, by implication, transcription level.

In a preferred embodiment, the expression of the target gene is measured by the polymerase chain reaction. In another embodiment, the expression of the target gene is measured using polyacrylamide gel analysis, chromatography or spectroscopy.

In another preferred embodiment, the expression of the target gene is measured by measuring the production of the encoded protein (measuring translation of the protein). Measurement of translation of a protein includes any suitable method for detecting and/or measuring proteins from a cell or cell extract. Such methods include, but are not limited to, immunoblot (*e.g.*, Western blot), enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunohistochemistry, immunofluorescence, fluorescence activated cell sorting (FACS) and immunofluorescence microscopy. Particularly preferred methods for detection of proteins include any single-cell assay, including immunohistochemistry and immunofluorescence assays. For example, one can use a detection agent, such as an antibody that specifically recognizes (selectively binds to) the protein encoded by the gene. Such methods are well known in the art.

Designing a compound for testing in a method of the present invention can include creating a new chemical compound or searching databases of libraries of known compounds (*e.g.*, a compound listed in a computational screening database containing three dimensional structures of known compounds). Designing can also be performed by simulating chemical compounds having substitute moieties at certain structural features. The step of designing can include selecting a chemical compound based on a known function of the compound. A preferred step of designing comprises computational screening of one or more databases of compounds in which the three dimensional structure of the compound is known and is interacted (*e.g.*, docked, aligned, matched, interfaced) with the three dimensional structure of a target by computer (*e.g.* as described by Humblet and Dunbar, *Animal Reports in Medicinal Chemistry*, vol. 28, pp. 275-283, 1993, M Venuti, ed., Academic Press). Methods to synthesize suitable chemical compounds are known to those of skill in the art and depend upon the structure of the chemical being synthesized. Methods to evaluate the bioactivity of the synthesized compound depend upon the bioactivity of the compound (*e.g.*, inhibitory or stimulatory).

Accordingly, in another embodiment of the invention, therapeutic compounds can be selected by determining the three-dimensional structure of a target; and determining or designing the three-dimensional structure of a therapeutic or regulatory compound by

rational drug design or detecting a structure that interacts with the target structure from a library of known compound structures. Preferably, the structure of the therapeutic compound is determined using computer software capable of modeling the interaction of a therapeutic compound with the target. One of skill in the art can select the appropriate three-dimensional structure, therapeutic or regulatory compound, and analytical software based on the identity of the target.

For example, suitable candidate chemical compounds can align to a subset of residues described for a target site. Preferably, a candidate chemical compound comprises a conformation that promotes the formation of covalent or noncovalent crosslinking between the target site and the candidate chemical compound. Preferably, a candidate chemical compound binds to a surface adjacent to a target site to provide an additional site of interaction in a complex. When designing an antagonist, for example, the antagonist should bind with sufficient affinity to the binding site or to substantially prohibit a ligand (*i.e.*, a molecule that specifically binds to the target site) from binding to a target area. It will be appreciated by one of skill in the art that it is not necessary that the complementarity between a candidate chemical compound and a target site extend over all residues specified here in order to inhibit or promote binding of a ligand.

In general, the design of a chemical compound possessing stereochemical complementarity can be accomplished by techniques that optimize, chemically or geometrically, the "fit" between a chemical compound and a target site. Such techniques are disclosed by, for example, Sheridan and Venkataraghavan, *Acc. Chem Res.*, vol. 20, p. 322, 1987: Goodford, *J. Med. Chem.*, vol. 27, p. 557, 1984; Beddell, *Chem. Soc. Reviews*, vol. 279, 1985; Hol, *Angew. Chem.*, vol. 25, p. 767, 1986; and Verlinde and Hol, *Structure*, vol. 2, p. 577, 1994, each of which are incorporated by this reference herein in their entirety.

As another example, a "geometric approach" is used. In a geometric approach, the number of internal degrees of freedom (and the corresponding local minima in the molecular conformation space) is reduced by considering only the geometric (hard sphere) interactions of two rigid bodies, where one body (the active site) contains "pockets" or "grooves" that form binding sites for the second body (the complementing molecule, such as a ligand). The geometric approach is described by Kuntz et al., *J. Mol. Biol.*, vol. 161, p. 269, 1982, which is incorporated by this reference herein in its entirety. The algorithm for chemical compound design can be implemented using the software

program DOCK Package, Version 1.0 (available from the Regents of the University of California). Pursuant to the Kuntz algorithm, the shape of the cavity or groove on the surface of a structure at a binding site or interface is defined as a series of overlapping spheres of different radii. One or more extant databases of crystallographic data (*e.g.*, the Cambridge Structural Database System maintained by University Chemical Laboratory, Cambridge University, Lensfield Road, Cambridge CB2 lEW, U.K.) or the Protein Data Bank maintained by Brookhaven National Laboratory, is then searched for chemical compounds that approximate the shape thus defined. Chemical compounds identified by the geometric approach can be modified to satisfy criteria associated with chemical complementarity, such as hydrogen bonding, ionic interactions or Van der Waals interactions.

As yet another example, one can determine the interaction of chemical groups ("probes") with an active site at sample positions within and around a binding site or interface, resulting in an array of energy values from which three dimensional contour surfaces at selected energy levels can be generated. This method is referred to herein as a "chemical-probe approach." The chemical-probe approach to the design of a chemical compound useful of the present invention is described by, for example, Goodford, *J. Med. Chem.*, vol. 28, p. 849, 1985, which is incorporated by this reference herein in its entirety, and is implemented using an appropriate software package, including for example, GRID (available from Molecular Discovery Ltd., Oxford OX2 9LL, U.K.). The chemical prerequisites for a site-complementing molecule can be identified at the outset, by probing the active site of a protein with different chemical probes, *e.g.*, water, a methyl group, an amine nitrogen, a carboxyl oxygen and/or a hydroxyl. Preferred sites for interaction between an active site and a probe are determined. Putative complementary chemical compounds can be generated using the resulting three dimensional patterns of such sites.

Candidate compounds identified or designed by the above-described methods can be synthesized using techniques known in the art, and depending on the type of compound. Synthesis techniques for the production of non-protein compounds, including organic and inorganic compounds are well known in the art. For example, for smaller peptides, chemical synthesis methods are preferred. For example, such methods include well known chemical procedures, such as solution or solid-phase peptide synthesis, or semi-synthesis in solution beginning with protein fragments coupled through

conventional solution methods. Such methods are well known in the art and may be found in general texts and articles in the area such as: Merrifield, 1997, *Methods Enzymol.* 289:3-13; Wade et al., 1993, *Australas Biotechnol.* 3(6):332-336; Wong et al., 1991, *Experientia* 47(11-12):1123-1129; Carey et al., 1991, *Ciba Found Symp.* 158:187-203; Plaue et al., 1990, *Biologicals* 18(3):147-157; Bodanszky, 1985, *Int. J. Pept. Protein Res.* 25(5):449-474; or H. Dugas and C. Penney, BIOORGANIC CHEMISTRY, (1981) at pages 54-92, all of which are incorporated herein by reference in their entirety. For example, peptides may be synthesized by solid-phase methodology utilizing a commercially available peptide synthesizer and synthesis cycles supplied by the manufacturer. One skilled in the art recognizes that the solid phase synthesis could also be accomplished using the FMOC strategy and a TFA/scavenger cleavage mixture. A compound that is a protein or peptide can also be produced using recombinant DNA technology and methods standard in the art, particularly if larger quantities of a protein are desired.

In still another embodiment of the invention, inhibitors of cell growth are identified by exposing a target to a candidate compound; measuring the binding of the candidate compound to the target; and selecting a compound that binds to the target at a desired concentration, affinity, or avidity. In a preferred embodiment, the assay is performed under conditions conducive to promoting the interaction or binding of the compound to the target. One of skill in the art can determine such conditions based on the target and the compound being used in the assay. In one embodiment, a BIAcore machine can be used to determine the binding constant of a complex between the target protein (a protein encoded by the target gene) and a natural ligand in the presence and absence of the candidate compound. For example, the target protein or a ligand binding fragment thereof can be immobilized on a substrate. A natural or synthetic ligand is contacted with the substrate to form a complex. The dissociation constant for the complex can be determined by monitoring changes in the refractive index with respect to time as buffer is passed over the chip (O'Shannessy et al. Anal. Biochem. 212:457-468 (1993); Schuster et al., Nature 365:343-347 (1993)). Contacting a candidate compound at various concentrations with the complex and monitoring the response function (*e.g.*, the change in the refractive index with respect to time) allows the complex dissociation constant to be determined in the presence of the test compound and indicates whether the candidate compound is either an inhibitor or an agonist of the complex. Alternatively, the

candidate compound can be contacted with the immobilized target protein at the same time as the ligand to see if the candidate compound inhibits or stabilizes the binding of the ligand to the target protein.

Other suitable assays for measuring the binding of a candidate compound to a target protein or for measuring the ability of a candidate compound to affect the binding of the target protein to another protein or molecule include, but are not limited to, Western blot, immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, microcytometry, microarray, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry. Other assays include those that are suitable for monitoring the effects of protein binding, including, but not limited to, cell-based assays such as: cytokine secretion assays, or intracellular signal transduction assays that determine, for example, protein or lipid phosphorylation, mediator release or intracellular $Ca^{++}$ mobilization.

In yet another embodiment, inhibitors of cellular growth are identified by exposing a target protein of the present invention (or a cell expressing the protein naturally or recombinantly) to a candidate compound and measuring the ability of the compound to inhibit (reduce, decrease, block) a biological activity of the protein. In one embodiment, the biological activity of a protein encoded by the target gene is measured by measuring the amount of product generated in a biochemical reaction mediated by the protein encoded by the target gene. In still another embodiment, the activity of the protein encoded by the target gene is measured by measuring the amount of substrate generated in a biochemical reaction mediated by the protein encoded by the target gene. In another embodiment, a biological activity is measured by measuring a specific event in a cell-based assay, such as release or secretion of a biological mediator or compound that is regulated by the activity of the target protein, measuring intracellular signal transduction assays that determine, for example, protein or lipid phosphorylation, mediator release or intracellular $Ca^{++}$ mobilization. Preferably, the activity of the protein is measured in the presence and absence of the candidate compound, or in the presence of another suitable control compound.

In one embodiment of the invention, when the protein encoded by a target gene is an enzyme, a therapeutic compound is identified by exposing the enzyme encoded by a target gene to a test compound; measuring the activity of the enzyme encoded by the target gene in the presence and absence of the compound; and selecting a compound that down-regulates or inhibits the activity of the enzyme encoded by the target gene. Methods to measure enzymatic activity are well known to those skilled in the art and are selected based on the identity of the enzyme being tested. For example, if the enzyme is a kinase, phosphorylation assays can be used.

In addition to methods for identifying and producing a biological compound that inhibits cell growth, the present invention includes methods known in the art that down-regulate expression or function of a target gene. For example, antisense RNA and DNA molecules may be used to directly block translation of mRNA encoded by these genes by binding to targeted mRNA and preventing protein translation. Polydeoxyribonucleotides can form sequence-specific triple helices by hydrogen bonding to specific complementary sequences in duplexed DNA to effect specific down-regulation of target gene expression. Formation of specific triple helices may selectively inhibit the replication or expression of a target gene by prohibiting the specific binding of functional trans-acting factors.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Within the scope of the invention are ribozyme embodiments including engineered hammerhead motif ribozyme molecules that specifically and efficiently catalyze endonucleolytic cleavage of RNA sequences. Antisense RNA molecules showing high-affinity binding to target sequences can also be used as ribozymes by addition of enzymatically active sequences known to those skilled in the art.

Polynucleotides to be used in triplex helix formation should be single-stranded and composed of deoxynucleotides. The base composition of these polynucleotides must be designed to promote triple helix formation via Hoogsteen base pairing rules, which generally require sizeable stretches of either purines or pyrimidines to be present on one strand of a duplex. Polynucleotide sequences may be pyrimidine-based, which will result in TAT and CGC triplets across the three associated strands of the resulting triple helix. The pyrimidine-rich polynucleotides provide base complementarity to a purine-rich region of a single strand of the duplex in a parallel orientation to that strand. In addition,

polynucleotides may be chosen that are purine-rich, for example, containing a stretch of G residues. These polynucleotides will form a triple helix with a DNA duplex that is rich in GC pairs, in which the majority of the purine residues are located on a single strand of the targeted duplex, resulting in GGC triplets across the three strands in the triplex.

Alternatively, sequences that can be targeted for triple helix formation can be increased by creating a so-called "switchback" polynucleotide. Switchback polynucleotides are synthesized in an alternating 5'-3', 3'-5' manner, so that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizeable stretch of either purines or pyrimidines to be present on one strand of a duplex.

Both antisense RNA and DNA molecules, and ribozymes of the invention may be prepared by any method known in the art. These include techniques for chemically synthesizing polynucleotides well known in the art such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into host cells.

Various modifications to the nucleic acid molecules may be introduced as a means of increasing intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences of ribonucleotides or deoxyribonucleotides to the 5' or 3' ends of the molecule or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the oligodeoxyribonucleotide backbone.

Preferably, methods used to identify therapeutic compounds are customized for each target gene or product. If the target product is an enzyme, then the enzyme will be expressed in cell culture and purified. The enzyme will then be screened *in vitro* against therapeutic compounds to look for inhibition of that enzymatic activity. If the target is a non-catalytic protein, then it will also be expressed and purified. Therapeutic compounds will then be tested for their ability to prevent, for example, the binding of a site-specific antibody or a target-specific ligand to the target product.

In a preferred embodiment, therapeutic compounds that bind to target products are identified, then those compounds can be further tested in biological assays that test for

characteristics such as apoptosis, tumor suppressor status (*e.g.*, p53 status), tumor cell growth and any other customary measure of anti-cancer activity.

In one embodiment of the invention, a therapeutic compound is not toxic to a human host cell. In another embodiment, the therapeutic compound is cytostatic or cytotoxic.

In one embodiment of the invention, a pharmaceutical composition is prepared from a therapeutically-effective amount of a therapeutic compound of the invention and a pharmaceutically-acceptable carrier. Pharmaceutically-acceptable carriers are well known to those with skill in the art. The pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, *e.g.*, by means of a conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. As used herein, a pharmaceutically acceptable carrier refers to any substance suitable for delivering a therapeutic composition useful in the method of the present invention to a suitable *in vivo* or *ex vivo* site. Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the compounds of the invention can be formulated in appropriate aqueous solutions, such as physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal and transcutaneous administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The compounds can be formulated for parenteral

administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

According to the present invention, an effective administration protocol (*i.e.*, administering a composition of the present invention in an effective manner) comprises suitable dose parameters and modes of administration that result in delivery of the compound or composition to a patient or to a target site, cell or tissue in the patient, and subsequent inhibition of the growth of the target cell, preferably so that the patient obtains some measurable, observable or perceived benefit from such administration. In some situations, where the target cell population is accessible for sampling, effective dose parameters can be determined using methods as described herein for assessment of tumor growth. Such methods include removing a sample of the target cell population from the patient prior to and after the compound or composition is administered, and measuring changes expression or biological activity of a target, as well as measuring inhibition of the growth of the cell. Alternatively, effective dose parameters can be determined by experimentation using *in vitro* cell cultures, *in vivo* animal models, and eventually, clinical trials if the patient is human. Effective dose parameters can be determined using methods standard in the art. Such methods include, for example, determination of

survival rates, side effects (*i.e.*, toxicity) and progression or regression of disease. Compounds which exhibit high therapeutic indices are preferred. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See, e.g.* Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch.1, p.1).

Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the inhibitory effects. Usual patient dosages for systemic administration range from 100 - 2000 mg/day. Stated in terms of patient body surface areas, usual dosages range from 50 - 910 mg/m$^2$/day. Usual average plasma levels should be maintained within 0.1-1000 μM. In cases of local administration or selective uptake, the effective local concentration of the compound can not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's body surface area, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

Suitable routes of administration can, for example, include oral, rectal, transmucosal, transcutaneous, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Alternatively, one can administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a specific tissue, often in a depot or sustained release formulation. Furthermore, one can administer the compound in a targeted drug delivery system, for example, in a liposome and/or conjugated with a cell-specific antibody. The liposomes and cell-specific antibody will be targeted to and taken up selectively by tumor cells.

Accordingly, a further embodiment of the invention is a method for inducing apoptosis in a cell by inhibiting a target of the present invention, *i.e.*, a target selected from the group consisting of any of the targets listed in Table 1 and/or represented by any of SEQ ID NOs:1-80. For example, this method can be conducted *in vivo* by administering to an individual an inhibitory or therapeutic compound as generally discussed herein. In addition, the method can be conducted *in vitro* or *ex vivo*.

A further embodiment of the present invention is a method for the diagnosis of a tumor or the monitoring of a tumor growth or regression or a tumor therapy in a patient. The methods include determining the level of a marker (also referred to as a biomarker) in a patient sample, wherein the marker is selected from any of the biomarkers listed in Table 1 or represented by any of SEQ ID NOs:1-80.

The first step of this method of the present invention includes detecting the expression or biological activity of a biomarker in a test sample from a patient (also called a patient sample). Suitable methods of obtaining a patient sample are known to a person of skill in the art. A patient sample can include any bodily fluid or tissue from a patient that may contain tumor cells or proteins of tumor cells. More specifically, according to the present invention, the term "test sample" or "patient sample" can be used generally to refer to a sample of any type which contains cells or products that have been secreted from cells to be evaluated by the present method, including but not limited to, a sample of isolated cells, a tissue sample and/or a bodily fluid sample. According to the present invention, a sample of isolated cells is a specimen of cells, typically in suspension or separated from connective tissue which may have connected the cells within a tissue *in vivo*, which have been collected from an organ, tissue or fluid by any suitable method which results in the collection of a suitable number of cells for evaluation by the method of the present invention. The cells in the cell sample are not necessarily of the same type, although purification methods can be used to enrich for the type of cells that are preferably evaluated. Cells can be obtained, for example, by scraping of a tissue, processing of a tissue sample to release individual cells, or isolation from a bodily fluid.

A tissue sample, although similar to a sample of isolated cells, is defined herein as a section of an organ or tissue of the body which typically includes several cell types and/or cytoskeletal structure which holds the cells together. One of skill in the art will appreciate that the term "tissue sample" may be used, in some instances, interchangeably with a "cell sample", although it is preferably used to designate a more complex structure than a cell sample. A tissue sample can be obtained by a biopsy, for example, including by cutting, slicing, or a punch. A bodily fluid sample, like the tissue sample, contains the cells to be evaluated for marker expression or biological activity and/or may contain a soluble biomarker that is secreted by cells, and is a fluid obtained by any method suitable for the particular bodily fluid to be sampled. Bodily fluids suitable for sampling include, but are not limited to, blood, mucous, seminal fluid, saliva, breast milk, bile and urine.

In general, the sample type (*i.e.*, cell, tissue or bodily fluid) is selected based on the accessibility and structure of the organ or tissue to be evaluated for tumor cell growth and/or on what type of cancer is to be evaluated. For example, if the organ/tissue to be evaluated is the breast, the sample can be a sample of epithelial cells from a biopsy (*i.e.*, a cell sample) or a breast tissue sample from a biopsy (a tissue sample). The sample that is most useful in the present invention will be cells, tissues or bodily fluids isolated from a patient by a biopsy or surgery or routine laboratory fluid collection.

Once a sample is obtained from the patient, the sample is evaluated for detection of the expression or biological activity of the biomarker of the present invention in the cells of the sample. Expression and biological activity of biomarkers of the invention and methods of detecting or measuring the same have been described in detail above with regard to the description of the use of the biomarkers as targets.

For example, the level of the marker can be determined by conventional methods such as expression assays to determine the level of expression of the gene, by biochemical assays to determine the level of the gene product, or by immunoassays. If appropriate, the marker can be identified as a cell surface molecule in tissue or in a bodily fluid, such as serum. For example, a patient sample, which can be immobilized, can be contacted with an antibody, or an antibody fragment, that selectively binds to the marker and determining whether the anti-marker antibody or fragment thereof has bound to the marker. As used herein, the term "selectively binds to" refers to the specific binding of one protein to another (*e.g.*, an antibody, fragment thereof, or binding partner to an antigen), wherein the level of binding, as measured by any standard assay (*e.g.*, an immunoassay), is statistically significantly higher than the background control for the assay. For example, when performing an immunoassay, controls typically include a reaction well/tube that contain antibody or antigen binding fragment alone (*i.e.*, in the absence of antigen), wherein an amount of reactivity (*e.g.*, non-specific binding to the well) by the antibody or antigen binding fragment thereof in the absence of the antigen is considered to be background. Binding can be measured using a variety of methods standard in the art, including, but not limited to: Western blot, immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, microcytometry,

microarray, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry. In a particular immunoassay, the marker level is determined using a first monoclonal antibody that binds specifically to the marker and a second antibody that binds to the first antibody.

In one embodiment, the amino acid sequence of a biomarker or the nucleic acid sequence of the corresponding gene can be used as a basis for detection. For example, detection can refer to detection of gene expression by determining the concentration of messenger RNA using common methods such as northern blot analysis, gene chip array analysis, Taqman analysis or other DNA/RNA hybridization platforms. The over or under expression of a biomarker can be an indication of the presence of a tumor or the predisposition for such tumor. Expression can be compared in patient samples versus samples isolated from healthy individuals.

In one embodiment of the method of the present invention, the level of a biomarker of the present invention is determined by determining the protein level of that biomarker in tissue. Suitable tissue tissues include tumor tissue and cell material obtained by biopsy.

In another embodiment of the method of the present invention, the level of a biomarker of the present invention is determined by determining a soluble form of a biomarker in a bodily fluid. Suitable bodily fluids include serum, ascitic or pleural fluid, serum being preferred. Levels of biomarker can be determined using various methods known in the art, including antibody binding assays, mass spectrometry analysis, 2-dimensional gel analysis and other methods used to quantify the presence of protein in solution. One preferred method of the present invention is to immobilize a biomarker to a solid substrate and then incubate the biomarker with a patient's serum. Bound antibodies to the biomarker are then detected by means of an enzyme-conjugated second antibody and a color reaction. Another preferred method is to immobilize an antibody that binds to a biomarker to a solid substrate and incubate the antibody with patient serum. Biomarker in the serum binds to the immobilized antibody and is detected using a second different antibody that binds to the biomarker and a color reaction. Another preferred method of the present invention is to contact an antibody that binds to a biomarker with a patient sample and then determining whether the antibody has been bound to the biomarker. Such method can be achieved using known methods including fluorescence cell sorter (FACS) analysis.

Suitable detection methods of a biomarker, an antibody that binds to a biomarker, or suitable nucleic acid probes, are known to those of skill in the art. The detection of biomarkers using antibodies is preferred, the same antibody being useful for both the soluble form and the form on the cell surface. Suitable antibodies for the method of the present invention include monoclonal antibodies, polyclonal antibodies, and fragments thereof. The antibody fragment refers to all parts of the antibody that bind to the biomarker including Fab, Fv or single-chain Fv fragments. Methods to produce such fragments are known to those of skill in the art. Preferred antibodies include monoclonal antibodies. Such antibodies can be produced using standard methods in the art.

Another method of the present invention can include immobilizing patient tissue in, for example, paraffin. The immobilized tissue can be sectioned and then contacted with an antibody that binds to a biomarker.

In the diagnostic/prognostic methods of the invention, if the level of the marker is greater than a normal level, the level of the marker is considered to be indicative of the presence of tumor cells. A normal level can be determined in a variety of ways. For example, if a patient history is known, a baseline level of the marker can be determined and higher levels will be indicative of tumor cells. Alternatively, a normal level can be based on the level for a healthy (*i.e.*, without tumor) individual in a given population. That is, a normal level can be based on a population having similar characteristics (*e.g.*, age, sex, race, medical history) as the patient in question.

More specifically, according to the present invention, a "baseline level" is a control level, and in some embodiments (but not all embodiments, depending on the method), a normal level, of biomarker expression or activity against which a test level of biomarker expression or biological activity (*i.e.*, in the test sample) can be compared. Therefore, it can be determined, based on the control or baseline level of biomarker expression or biological activity, whether a sample to be evaluated for tumor cell growth has a measurable increase, decrease, or substantially no change in biomarker expression or biological activity, as compared to the baseline level. In one aspect, the baseline level can be indicative of the cell growth expected in a normal (*i.e.*, healthy, negative control, non-tumor) cell sample. Therefore, the term "negative control" used in reference to a baseline level of biomarker expression or biological activity typically refers to a baseline level established in a sample from the patient or from a population of individuals which is believed to be normal (*i.e.*, non-tumorous, not undergoing neoplastic transformation, not

exhibiting inappropriate cell growth). It is noted that the "negative control" most typically has a lower level of biomarker expression or activity than would be detected in an experimental cell having inappropriate, increased cell growth, because the expression/biological activity of the biomarkers described herein are correlated with cell growth in most tumor cell types. In another embodiment, a baseline can be indicative of a positive diagnosis of tumor cell growth. Such a baseline level, also referred to herein as a "positive control" baseline, refers to a level of biomarker expression or biological activity established in a cell sample from the patient, another patient, or a population of individuals, wherein the sample was believed, based on data for that cell sample, to be neoplastically transformed (*i.e.*, tumorous, exhibiting inappropriate cell growth, cancerous). It is noted that this "positive control" will most typically have a higher level of biomarker expression or activity than in a normal cell, again due to the correlative relationship between the biomarkers of the present invention and cell growth in the majority of tumor cells. In yet another embodiment, the baseline level can be established from a previous sample from the patient being tested, so that the tumor growth of a patient can be monitored over time and/or so that the efficacy of a given therapeutic protocol can be evaluated over time. Methods for detecting biomarker expression or biological activity are described in detail above.

The method for establishing a baseline level of biomarker expression or activity is selected based on the sample type, the tissue or organ from which the sample is obtained, the status of the patient to be evaluated, and, as discussed above, the focus or goal of the assay (*e.g.*, diagnosis, staging, monitoring). Preferably, the method is the same method that will be used to evaluate the sample in the patient. In a most preferred embodiment, the baseline level is established using the same cell type as the cell to be evaluated.

In one embodiment, the baseline level of biomarker expression or biological activity is established in an autologous control sample obtained from the patient. The autologous control sample can be a sample of isolated cells, a tissue sample or a bodily fluid sample, and is preferably a cell sample or tissue sample. According to the present invention, and as used in the art, the term "autologous" means that the sample is obtained from the same patient from which the sample to be evaluated is obtained. The control sample should be of or from the same cell type and preferably, the control sample is obtained from the same organ, tissue or bodily fluid as the sample to be evaluated, such that the control sample serves as the best possible baseline for the sample to be evaluated.

In one embodiment, when the goal of the assay is diagnosis of abnormal cell growth, it is desirable to take the control sample from a population of cells, a tissue or a bodily fluid which is believed to represent a "normal" cell, tissue, or bodily fluid, or at a minimum, a cell or tissue which is least likely to be undergoing or potentially be predisposed to develop tumor cell growth. For example, if the sample to be evaluated is an area of apparently abnormal cell growth, such as a tumorous mass, the control sample is preferably obtained from a section of apparently normal tissue (*i.e.*, an area other than and preferably a reasonable distance from the tumorous mass) in the tissue or organ where the tumorous mass is growing. In one aspect, if a tumor to be evaluated is in the colon, the test sample would be obtained from the suspected tumor mass and the control sample would be obtained from a different section of the colon, which is separate from the area where the mass is located and which does not show signs of uncontrolled cellular proliferation.

In another embodiment, when the goal is to monitor tumor cell growth in the patient, the autologous baseline sample is typically a previous sample from the patient which was taken from an apparent or confirmed tumorous mass, and/or from apparently normal (*i.e.*, non-tumor) tissue in the patient (or a different type of baseline for normal can be used, as discussed below).

Therefore, a second method for establishing a baseline level of biomarker expression or biological activity is to establish a baseline level of biomarker expression or biological activity from at least one measurement of biomarker expression or biological activity in a previous sample from the same patient. Such a sample is also an autologous sample, but is taken from the patient at a different time point than the sample to be tested. Preferably, the previous sample(s) were of a same cell type, tissue type or bodily fluid type as the sample to be presently evaluated. In one embodiment, the previous sample resulted in a negative diagnosis (*i.e.*, no tumor cell growth, or potential therefore, was identified). In this embodiment, a new sample is evaluated periodically (*e.g.*, at annual physicals), and as long as the patient is determined to be negative for tumor development, an average or other suitable statistically appropriate baseline of the previous samples can be used as a "negative control" for subsequent evaluations. For the first evaluation, an alternate control can be used, as described below, or additional testing may be performed to confirm an initial negative diagnosis, if desired, and the value for biomarker expression or biological activity can be used thereafter. This type of baseline control is frequently

used in other clinical diagnosis procedures where a "normal" level may differ from patient to patient and/or where obtaining an autologous control sample at the time of diagnosis is not possible, not practical or not beneficial. For example, for a patient who has periodic mammograms, the previous mammograms serve as baseline controls for the mammary tissue of the individual patient. Similarly, for a patient who is regularly screened for prostate cancer by evaluation of levels of prostate cancer antigen (PCA), previous PCA levels are frequently used as a baseline for evaluating whether the individual patient experiences a change.

In another embodiment, the previous sample from the patient resulted in a positive diagnosis (*i.e.*, tumor growth was positively identified). In this embodiment, the baseline provided by the previous sample is effectively a positive control for tumor growth, and the subsequent samplings of the patient are compared to this baseline to monitor the progress of the tumor growth and/or to evaluate the efficacy of a treatment which is being prescribed for the cancer. In this embodiment, it may also be beneficial to have a negative baseline level of biomarker expression or biological activity (*i.e.*, a normal cell baseline control), so that a baseline for remission or regression of the tumor can be set. Monitoring of a patient's tumor growth can be used by the clinician to modify cancer treatment for the patient based on whether an increase or decrease in cell growth is indicated.

It will be clear to those of skill in the art that some samples to be evaluated will not readily provide an obvious autologous control sample, or it may be determined that collection of autologous control samples is too invasive and/or causes undue discomfort to the patient. In these instances, an alternate method of establishing a baseline level of biomarker expression or biological activity can be used, examples of which are described below.

Another method for establishing a baseline level of biomarker expression or biological activity is to establish a baseline level of biomarker expression or biological activity from control samples, and preferably control samples that were obtained from a population of matched individuals. It is preferred that the control samples are of the same sample type as the sample type to be evaluated for biomarker expression or biological activity (*e.g.*, the same cell type, and preferably from the same tissue or organ). According to the present invention, the phrase "matched individuals" refers to a matching of the control individuals on the basis of one or more characteristics which are suitable

for the type of cell or tumor growth to be evaluated. For example, control individuals can be matched with the patient to be evaluated on the basis of gender, age, race, or any relevant biological or sociological factor that may affect the baseline of the control individuals and the patient (*e.g.*, preexisting conditions, consumption of particular substances, levels of other biological or physiological factors). To establish a control or baseline level of biomarker expression or biological activity, samples from a number of matched individuals are obtained and evaluated for biomarker expression or biological activity. The sample type is preferably of the same sample type and obtained from the same organ, tissue or bodily fluid as the sample type to be evaluated in the test patient. The number of matched individuals from whom control samples must be obtained to establish a suitable control level (*e.g.*, a population) can be determined by those of skill in the art, but should be statistically appropriate to establish a suitable baseline for comparison with the patient to be evaluated (*i.e.*, the test patient). The values obtained from the control samples are statistically processed using any suitable method of statistical analysis to establish a suitable baseline level using methods standard in the art for establishing such values.

A baseline such as that described above can be a negative control baseline, such as a baseline established from a population of apparently normal control individuals. Alternatively, as discussed above, such a baseline can be established from a population of individuals that have been positively diagnosed as having cancer, and particularly, cancer of a specified stage, as set forth by the medical community, so that one or more baseline levels can be established for use in staging a cancer in the patient to be evaluated. Therefore, in one embodiment, the baseline level is one or more tumor control samples that are correlated with a particular stage of tumor development for that type of tumor. For example, tumor samples from an appropriate number of individuals that have been diagnosed as having a particular stage of a given cancer (*e.g.*, Stage I colon cancer) are tested for biomarker expression or biological activity. The values obtained from these control samples are statistically processed to establish a suitable baseline level using methods standard in the art for establishing such values, and the baseline is noted as being indicative of that particular stage of cancer. Preferably, a similar value is determined for each of the established stages of the given cancer, so that a panel of baseline values, each representing a different stage of the cancer, is formed. The level of biomarker expression or biological activity in the patient sample is then compared to each of the baseline levels

to determine to which baseline the biomarker level of the patient is statistically closest. It will be appreciated that a given patient sample may fall between baseline levels of two different stages such that the best diagnosis is that the patient tumor is at least at the lower stage, but is perhaps in the process of advancing to the higher stage. The data provided by this method can be used in conjunction with current cancer staging methods to assist the physician in the evaluation of the patient and in prescribing suitable treatment for the cancer.

It will be appreciated by those of skill in the art that a baseline need not be established for each assay as the assay is performed but rather, a baseline can be established by referring to a form of stored information regarding a previously determined baseline level of biomarker expression for a given control sample, such as a baseline level established by any of the above-described methods. Such a form of stored information can include, for example, but is not limited to, a reference chart, listing or electronic file of population or individual data regarding "normal" (negative control) or tumor positive (including staged tumors) biomarker expression; a medical chart for the patient recording data from previous evaluations; or any other source of data regarding baseline biomarker expression that is useful for the patient to be diagnosed.

After the level of biomarker expression or biological activity is detected in the sample to be evaluated for tumor cell growth, such level is compared to the established baseline level of biomarker expression or biological activity, determined as described above. Also, as mentioned above, preferably, the method of detecting used for the sample to be evaluated is the same or qualitatively and/or quantitatively equivalent to the method of detecting used to establish the baseline level, such that the levels of the test sample and the baseline can be directly compared. In comparing the test sample to the baseline control, it is determined whether the test sample has a measurable decrease or increase in biomarker expression or biological activity over the baseline level, or whether there is no statistically significant difference between the test and baseline levels. After comparing the levels of biomarker expression or biological activity in the samples, the final step of making a diagnosis, monitoring, or staging of the patient can be performed as discussed above.

According to the present invention, detection of an increased level of biomarker expression or biological activity in the sample to be evaluated (*i.e.*, the test sample) as compared to the baseline level indicates that, as compared to the baseline sample,

increased cell growth or tumorigenicity or a potential therefore is indicated in the cells corresponding to the test sample. This indication of increased tumorigenicity is evaluated based on what the baseline represents, and can mean: (1) a positive diagnosis of tumorigenicity (*i.e.*, neoplastic transformation) or potential for tumor cell growth in the patient; (2) continued or increased tumorigenicity in a patient previously diagnosed with a cancer; and/or (3) a higher stage of tumorigenicity than that represented by the baseline. More specifically, if the baseline is a normal or negative control sample (*i.e.*, autologous or otherwise established, such as from a population control), a detection of increased biomarker expression or biological activity in the test sample as compared to the control sample indicates that the cells in the test sample are undergoing (or are at risk of undergoing) increased, and likely inappropriate (*i.e.*, tumorous, neoplastic) cell growth. If the baseline sample is a previous sample from the patient (or a population control) and is representative of a positive diagnosis of tumor cell growth in the patient (*i.e.*, a positive control), a detection of increased biomarker expression or biological activity in the sample as compared to the baseline may indicate that the cells in the test sample are experiencing increased tumor growth or a potential therefore, which would suggest to a clinician that a treatment currently being prescribed, for example, is not controlling the tumor growth or that tumor growth in the patient has recurred. If the baseline sample is representative of a particular stage of tumor, a detection of increased biomarker expression or biological activity in the sample as compared to the baseline may indicate that the cells in the test sample are at a higher stage of tumor growth than the stage represented by the baseline sample.

Similarly, detection of a decreased level of biomarker expression or biological activity in the sample to be evaluated (*i.e.*, the test sample) as compared to the baseline level indicates that, as compared to the baseline sample, decreased cell growth or tumorigenicity or a potential therefore is indicated in the test cells. This indication of decreased tumorigenicity is evaluated based on what the baseline represents, and can mean: (1) a negative diagnosis of tumorigenicity (neoplastic transformation) or potential for tumor cell growth in the patient; (2) reduced tumorigenicity in a patient previously diagnosed with a cancer; and/or (3) a lower stage of tumorigenicity than that represented by the baseline. More specifically, if the baseline is a normal or negative control (autologous or otherwise established, such as from a population control), a detection of decreased biomarker expression or biological activity in the test sample as compared to

the control sample indicates that the cells in the test sample are also normal and are not predicted to be at risk of undergoing inappropriate (*i.e.*, tumorous, neoplastic) cell growth. If the baseline sample is a previous sample from the patient (or from a population control) and is representative of a positive diagnosis of tumorigenicity in the patient (*i.e.*, a positive control), a detection of decreased biomarker expression or biological activity in the sample as compared to the baseline indicates that the cells in the test sample are experiencing decreased tumorigenicity or a potential therefore, which suggests to a clinician, for a patient that has cancer, that a treatment currently being prescribed, for example, is successfully controlling the tumor growth or that a tumor in the patient is in remission or eliminated. If the baseline sample is representative of a particular stage of tumor, a detection of decreased biomarker expression or biological activity in the sample as compared to the baseline indicates that the cells in the test sample are at a lower stage of tumor growth than the stage represented by the baseline sample.

Finally, detection of biomarker expression that is not statistically significantly different than the biomarker expression or biological activity in the baseline sample indicates that, as compared to the baseline sample, no difference in tumorigenicity or a potential therefore is indicated in the test cells. This indication of effectively a "baseline level" of cell growth in the test cell is evaluated based on what the baseline represents, and can mean: (1) a negative or positive diagnosis of tumorigenicity (neoplastic transformation) or potential therefore in the patient; (2) unchanged tumorigenicity in a patient previously diagnosed with a cancer; and/or (3) a correlation with a stage of tumor growth that is represented by the baseline. More specifically, if the baseline is a normal or negative control (autologous or otherwise established, such as from a population control), detection of biomarker expression or biological activity in the test sample that is not statistically significantly different than the baseline sample indicates that the cells in the test sample are also normal and are not predicted to be at risk of undergoing inappropriate (*i.e.*, tumorous, neoplastic) cell growth. If the baseline sample is a previous sample from the patient (or from a population control) and is representative of a positive diagnosis of tumor cell growth in the patient (*i.e.*, a positive control), a detection of biomarker expression or biological activity in the sample that is not statistically significantly different than the baseline indicates that the cells in the test sample are experiencing tumor cell growth or a potential therefore, and the patient should be further

evaluated for cancer. In a patient who has cancer and is being monitored for tumor progression, a detection of biomarker expression or biological activity in the test sample that is not statistically significantly different than the baseline sample indicates that the tumor is neither increasing (progressing) nor decreasing (regressing). Such a diagnosis might suggest to a clinician that a treatment currently being prescribed, for example, is ineffective in controlling the tumor growth or is preventing accelerated tumor growth, but is not causing tumor growth to regress. Finally, if the baseline sample is representative of a particular stage of tumor, a detection of biomarker expression or biological activity in the test sample that is not statistically significantly different than the baseline sample indicates that the cells in the test sample are at substantially the same stage of tumor growth as the stage represented by the baseline sample.

As discussed above, a positive diagnosis indicates that increased cell growth, and possibly tumor cell growth (neoplastic transformation), has occurred, is occurring, or is statistically likely to occur in the cells or tissue from which the sample was obtained. In order to establish a positive diagnosis, the level of biomarker activity is increased over the established baseline by an amount that is statistically significant (*i.e.*, with at least a 95% confidence level, or $p<0.05$). Preferably, detection of at least about a 10% change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased cell growth for said sample, as compared to the baseline. More preferably, detection of at least about a 30% change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased cell growth for said sample, as compared to the baseline. More preferably, detection of at least about a 50% change, and more preferably at least about a 70% change, and more preferably at least about a 90% change, or any percentage change between 5% and higher in 1% increments (*i.e.*, 5%, 6%, 7%, 8%...) in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased tumorigenicity for said sample. In one embodiment, a 1.5 fold change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased tumorigenicity for said sample. More preferably, detection of at least about a 3 fold change, and more preferably at least about a 6 fold change, and even more preferably, at least about a 12 fold change, and even more preferably, at least about a 24 fold change, or any fold change from 1.5 up in increments of 0.5 fold (*i.e.*, 1.5, 2.0, 2.5, 3.0...) in biomarker expression or biological

activity as compared to the baseline level, results in a positive diagnosis of increased tumorigenicity for said sample.

This method of diagnosis can be used specifically to determine the prognosis for cancer in the patient or to determine the susceptibility of the patient to a therapeutic treatment. In some embodiments, the method may be useful to monitor the progress of a patient undergoing therapeutic treatment for a tumor.

The present invention also includes a kit that utilizes the diagnostic methods of the present invention. The kit preferably contains any means of detecting the expression or activity of a biomarker of the present invention in a test sample, and preferably includes a probe, PCR primers, or an antibody, antigen binding peptide, or fragment thereof, that binds to a biomarker. The kit can include any reagent needed to perform a diagnostic method envisioned herein. The antibody, or fragment thereof, can be conjugated to another unit, for example a marker or immobilized to a solid carrier (substrate). The kit can also contain a second antibody for the detection of biomarker:antibody complexes. In one embodiment, the kit can contain a means for detecting a control marker characteristic of a cell type in the test sample. The antibody, or fragment thereof, may be present in free form or immobilized to a substrate such as a plastic dish, a test tube, a test rod and so on. The kit can also include suitable reagents for the detection of and/or for the labeling of positive or negative controls, wash solutions, dilution buffers and the like.

More specifically, according to the present invention, a means for detecting biomarker expression or biological activity can be any suitable reagent that can be used in a method for detection of biomarker expression or biological activity as described previously herein. Such reagents include, but are not limited to: a probe that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding the biomarker or a fragment thereof (including to a biomarker-specific regulatory region in the biomarker-encoding gene); RT-PCR primers for amplification of mRNA encoding the biomarker or a fragment thereof; and/or an antibody, antigen-binding fragment thereof or other antigen-binding peptide that selectively binds to the biomarker.

According to the present invention, a probe is a nucleic acid molecule which typically ranges in size from about 8 nucleotides to several hundred nucleotides in length. Such a molecule is typically used to identify a target nucleic acid sequence in a sample by hybridizing to such target nucleic acid sequence under stringent hybridization conditions. Hybridization conditions have been described in detail above.

PCR primers are also nucleic acid sequences, although PCR primers are typically oligonucleotides of fairly short length which are used in polymerase chain reactions. PCR primers and hybridization probes can readily be developed and produced by those of skill in the art, using sequence information from the target sequence. (See, for example, Sambrook et al., *supra* or Glick et al., *supra*).

Antibodies that selectively bind to a biomarker in the sample can be produced using information available in the art. Antibodies useful in the assay kit and methods of the present invention can include polyclonal and monoclonal antibodies, divalent and monovalent antibodies, bi- or multi-specific antibodies, serum containing such antibodies, antibodies that have been purified to varying degrees, and any functional equivalents of whole antibodies. Isolated antibodies of the present invention can include serum containing such antibodies, or antibodies that have been purified to varying degrees. Whole antibodies of the present invention can be polyclonal or monoclonal. Alternatively, functional equivalents of whole antibodies, such as antigen binding fragments in which one or more antibody domains are truncated or absent (*e.g.*, Fv, Fab, Fab', or $F(ab)_2$ fragments), as well as genetically-engineered antibodies or antigen binding fragments thereof, including single chain antibodies or antibodies that can bind to more than one epitope (*e.g.*, bi-specific antibodies), or antibodies that can bind to one or more different antigens (*e.g.*, bi- or multi-specific antibodies), may also be employed in the invention.

Genetically engineered antibodies include those produced by standard recombinant DNA techniques involving the manipulation and re-expression of DNA encoding antibody variable and/or constant regions. Particular examples include, chimeric antibodies, where the $V_H$ and/or $V_L$ domains of the antibody come from a different source to the remainder of the antibody, and CDR grafted antibodies (and antigen binding fragments thereof), in which at least one CDR sequence and optionally at least one variable region framework amino acid is (are) derived from one source and the remaining portions of the variable and the constant regions (as appropriate) are derived from a different source. Construction of chimeric and CDR-grafted antibodies is described, for example, in European Patent Applications: EP-A 0194276, EP-A 0239400, EP-A 0451216 and EP-A 0460617.

Generally, in the production of an antibody, a suitable experimental animal, such as, for example, but not limited to, a rabbit, a sheep, a hamster, a guinea pig, a mouse, a

rat, or a chicken, is exposed to an antigen against which an antibody is desired. Typically, an animal is immunized with an effective amount of antigen that is injected into the animal. An effective amount of antigen refers to an amount needed to induce antibody production by the animal. The animal's immune system is then allowed to respond over a pre-determined period of time. The immunization process can be repeated until the immune system is found to be producing antibodies to the antigen. In order to obtain polyclonal antibodies specific for the antigen, serum is collected from the animal that contains the desired antibodies (or in the case of a chicken, antibody can be collected from the eggs). Such serum is useful as a reagent. Polyclonal antibodies can be further purified from the serum (or eggs) by, for example, treating the serum with ammonium sulfate.

Monoclonal antibodies may be produced according to the methodology of Kohler and Milstein (*Nature* 256:495-497, 1975). For example, B lymphocytes are recovered from the spleen (or any suitable tissue) of an immunized animal and then fused with myeloma cells to obtain a population of hybridoma cells capable of continual growth in suitable culture medium. Hybridomas producing the desired antibody are selected by testing the ability of the antibody produced by the hybridoma to bind to the desired antigen.

The invention also extends to non-antibody polypeptides, sometimes referred to as antigen binding partners or antigen binding peptides, which have been designed to bind selectively to the protein of interest (a biomarker). Examples of the design of such polypeptides, which possess a prescribed ligand specificity, are given in Beste et al. (*Proc. Natl. Acad. Sci.* 96:1898-1903, 1999), incorporated herein by reference in its entirety.

In one embodiment, a means for detecting a control marker that is characteristic of the cell type being sampled can generally be any type of reagent that can be used in a method of detecting the presence of a known marker in a sample, such as by a method for detecting the presence of a biomarker described previously herein. Specifically, the means is characterized in that it identifies a specific marker of the cell type being analyzed that positively identifies the cell type. For example, in a breast tumor assay, it is desirable to screen breast epithelial cells for the level of the biomarker expression and/or biological activity. Therefore, the means for detecting a control marker identifies a marker that is characteristic of an epithelial cell and preferably, a breast epithelial cell, so

that the cell is distinguished from other cell types, such as a fibroblast. Such a means increases the accuracy and specificity of the assay of the present invention. Such a means for detecting a control marker include, but are not limited to: a probe that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding a protein marker; PCR primers which amplify such a nucleic acid molecule; and/or an antibody, antigen binding fragment thereof, or antigen binding peptide that selectively binds to the control marker in the sample. Nucleic acid and amino acid sequences for many cell markers are known in the art and can be used to produce such reagents for detection.

The means for detecting a biomarker and/or a control marker of the assay kit of the present invention can be conjugated to a detectable tag or detectable label. Such a tag can be any suitable tag which allows for detection of the reagents used to detect the biomarker or control marker and includes, but is not limited to, any composition or label detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads (*e.g.*, Dynabeads™), fluorescent dyes (*e.g.*, fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (*e.g.*, $^{3}H$, $^{125}I$, $^{35}S$, $^{14}C$, or $^{32}P$), enzymes (*e.g.*, horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (*e.g.*, polystyrene, polypropylene, latex, etc.) beads.

In addition, the means for detecting of the assay kit of the present invention can be immobilized on a substrate. Such a substrate can include any suitable substrate for immobilization of a detection reagent such as would be used in any of the previously described methods of detection. Briefly, a substrate suitable for immobilization of a means for detecting includes any solid support, such as any solid organic, biopolymer or inorganic support that can form a bond with the means for detecting without significantly effecting the activity and/or ability of the detection means to detect the desired target molecule. Exemplary organic solid supports include polymers such as polystyrene, nylon, phenol-formaldehyde resins, acrylic copolymers (*e.g.*, polyacrylamide), stabilized intact whole cells, and stabilized crude whole cell/membrane homogenates. Exemplary biopolymer supports include cellulose, polydextrans (*e.g.*, Sephadex®), agarose, collagen and chitin. Exemplary inorganic supports include glass beads (porous and nonporous),

stainless steel, metal oxides (*e.g.*, porous ceramics such as $ZrO_2$, $TiO_2$, $Al_2O_3$, and NiO) and sand.

According to the present invention, the method and assay for assessing the tumorigenicity of cells in a patient, as well as other methods disclosed herein, are suitable for use in a patient or cells from a patient or host that is a member of the Kingdom, Animalia, and particularly of the Vertebrate class, Mammalia, including, without limitation, primates, livestock and domestic pets (*e.g.*, a companion animal). Most typically, a patient will be a human patient or host cells will be derived from human patients, although the use of the methods of the invention in any suitable non-human animal model or host cell is also encompassed.

All publications cited herein are incorporated by reference in their entirety.

The Examples, which follow, are illustrative of specific embodiments of the invention, and various uses thereof. They are set forth for explanatory purposes only, and are not to be taken as limiting the invention.

## EXAMPLES

Example 1

The purpose of this experiment was to perform a nearly saturated genome wide GSE screen in a tumor cell line model for GSEs that protect cells against apoptosis.

### 1. V98 Vector Design and Construction

Vector V98 was created through modification of p610SL, a derivative of $pLNCO_3$ (B-D Chang and I.B. Roninson, Gene 183 (1996) 137-142.) A schematic of V98 is shown in Figure 1. The region flanking the multiple cloning site (MCS) downstream of the inducible CMV promoter was re-engineered (1) to introduce restriction endonuclease sites for enzymes expected to occur with low frequency in the human genome [*e.g.*, Fse I (1 per 170 kBp), Mlu I (1 per 300 kBp), and Rsr II (1 per 260 kBp)], (2) to introduce a short sequence of nucleic acid containing stop codons in all three DNA reading frames downstream of the MCS, (3) to introduce between the Fse I and Mlu I sites on the re-engineered vector backbone a Kozak sequence for efficient translation initiation of peptides encoded by random fragments cloned into the MCS (4) to introduce sequences complementary to well established DNA primers used for DNA sequencing (*e.g.*, M13F-20 and M13R), to permit rapid and efficient sequencing of inserts cloned into the MCS, (5) to introduce sequences flanking the MCS, derived from the genome of *Zea mays*, and

(6) to introduce into the MCS a "stuffer" fragment of about 2.2 kBp, which permits easy assessment of the completeness of vector digestion and selection of the appropriate backbone fragment during vector preparation.

A cDNA encoding the open reading frame of the murine Lyt-2-alpha' gene was recovered from Marathon ready mouse spleen cDNA (Clontech) using PCR with the following conditions: 5 μL of marathon ready cDNA, 5 μL 10X cDNA PCR buffer, 1 μL 10 mM dNTP mix, 1 μL Advantage 2 polymerase mix (Clontech, #8430-1), 1 μL of 10 μM upstream primer 5'- ACC ATG GCC TCA CCG TTG ACC CGC TTT -3' (SEQ ID NO:81), 1 μL or 10 μM downstream primer 5'- CTA GCG GCT GTG GTA GCA GAT GAG A -3' (SEQ ID NO:82), and 36 μL of water. Cycling parameters were: 94°C for 3 min.; followed by 30 cycles of 94°C for 30 sec., 55°C for 30 sec., and 72°C for 2 minutes; followed by 72°C for 10 minutes; followed by a 4°C soak. The resultant PCR product of 669 nucleotides was subcloned into a pCRII TOPO vector (InVitrogen). Several independent clones were sequenced to confirm no mutations were introduced in the Lyt-2-alpha' ORF by the PCR. One pCRII-TOPO-Lyt-2-alpha' clone was shown to be free of mutations, clone #2. DNA from clone #2 was subjected to a second round of PCR (Vt = 50 μL) using the following conditions: 1 ng plasmid DNA, 5 μL 10X cDNA PCR buffer, 0.8 μL of 10 mM dNTP mix, 1 μL of Advantage 2 polymerase mix (Clontech, #8430-1), 2.5 μL of 10 μM upstream primer 5'- CTA CGG ATC CAC CAT GGC CTC ACC GTT GA -3' (SEQ ID NO:83) and 2.5 μL of 10 μM downstream primer 5'- GTA CAT CGA TCT AGC GGC TGT GGT AGC AGA TGA GA -3' (SEQ ID NO:84). These primers permitted recovery the ORF of the Lyt-2-alpha' gene flanked by BamH I (upstream) and Cla I restriction endonuclease sites. Cycling parameters were: 94°C for 3 min.; followed by 30 cycles of 94°C for 30 sec., 55°C for 30 sec., and 72°C for 2 minutes; followed by 72°C for 10 minutes; followed by a 4°C soak. The resulting 689-bp PCR product was purified from surrounding proteins and salts using a Qiagen PCR clean up kit following manufacturer's instructions. The purified Clone #2 DNA digested with Bam HI restriction endonuclease (NEB, #R0136S). The digested product was purified using a Qiagen PCR clean up kit and the buffer was changed. The digested DNA was then further digested with Cla I restriction endonuclease (NEB, #R0197S). The doubly restricted Clone #2 DNA was then subcloned into the backbone fragment of the 610SL retroviral vector produced by double digestion of 610SL with Bcl I (NEB, #R0160S) and

Sfu I (Roche, #1243497) restriction endonucleases. Sequencing of DNA harvested from several independent bacterial colonies that were produced from this subcloning step yielded a clone that showed no mutations in the Lyt-2-alpha' ORF. This clone was named V97.

The modifications to the MCS regions of vector 610SL were created by sequential cloning of various double stranded oligonucleotides containing the desired sequences into several precursor plasmids. Sequences designed to be located 5' to the Fse I GSE cloning site in V98, *e.g.*, M13F-20 primer site, primer site for P1X, were created by subcloning annealed oligonucleotides 5'- AGC TGT AAA ACG ACG GCC AGT GAG CGT TTA AAC GAA TTC CAG ACT AGT GGC CGG CCG TGC A -3' (SEQ ID NO:85) and 5'- CGG CCG GCC ACT AGT CTG GAA TTC GTT TAA ACG CTC ACT GGC CGT CGT TTT AC -3' (SEQ ID NO:86) into the vector pEFGP-1 (ClonTech) between the HinD III and Pst I sites, to create pEGFP5'. The duplex produced by annealing primers 5'- AAT TCT GCA GCC CAG GTA AAA TTC GCT AGC CT -3' (SEQ ID NO:87) and 5'- CTA GAG GCT AGC GAA TTT TAC CTG GGC TGC AG -3' (SEQ ID NO:88), which contains the priming site for P1X sequence, was subcloned between the Eco RI and Spe I sites of pEGFP5' to yield pEGFP54. The modified 5' region of the MCS was recovered from plasmid pEFGP54 as a Bgl II – Not I flanked fragment, and subcloned between the Bgl II and Not I sites of p610SL, to yield p610-E54P1. Sequences designed to be located 3' to the Rsr II GSE cloning site in V98, *e.g.*, 3 frame stop cassette, primer P2X, M13R sequencing primer, were created by subcloning of annealed oligonucleotides 5'- CGG TCC GTG AGT GAG TGA GGC GCG CC G GAT CCT AAC CTA GGT AAT CAT GGT CAT AGC TGT TTC CTG CAG GGC -3' (SEQ ID NO:89) and 5'- GGC CGC CCT GCA GGA AAC AGC TAT GAC CAT GAT TAC CTA GGT TAG GAT CCG GCG CGC CTC ACT CAC TCA CGG ACC GTG CA -3' (SEQ ID NO:90) into the vector pBlueScript II (Stratagene) between the Pst I and Not I sites, to create plasmid pBS3.3'. The duplex produced by annealing primers 5'- GAT CCC GGG TCG TGT ATT CAG CTT TCC TTG TTC CT -3' (SEQ ID NO:91) and 5'- CTA GAG GAA CAA GGA AAG CTG AAT ACA CGA CCC GG -3' (SEQ ID NO:92), which contains the priming site for P2X sequence, was subcloned between the BamH I and Avr II sites of pBS3.3' to yield pBS3.3'P12.

The stuffer fragment for V98 was designed to contain a luciferase ORF joined to a prokaryotic blasticidin S transferase (bsd) expression cassette, in order to yield a 2.2 kBp

DNA fragment. The luciferase ORF and was created by PCR using the following primers 5'- CAT CAA GCT TGG CCG GCC ACC ATG GAC GCG TCC GAA GAC GCC AAA AAC ATA AAG -3' (SEQ ID NO:93) and 5'- CAC GTG GAT ATC TTA CAA TTT GGA CTT TCC GCC CT -3' (SEQ ID NO:94) to amplify the luciferase ORF from the plasmid pNFκB-luc (Strategene, #219078), while the bsd expression cassette was created by PCR using the primers 5'- TTG TAA GAT ATC CAC GTG TTG ACA ATT AAT C -3' (SEQ ID NO:95) and 5'- CAT CAG ATC TGT CGA CCG GAC CGA CGC GTC CAC GAA GTG CTT AGC -3' (SEQ ID NO:96) to amplify the E7-blasticindin S transferase open reading frame cassette from plasmid EM7-bsd. (InVitrogen, #V511-20). Both reactions were performed using the following cycling parameters: 95°C for 3 min; followed by 30 cycles of 94°C for 30 sec., 60°C for 30 sec., 72°C for 2 min.; followed by 72°C for 10 min.; followed by a soak at 4°C. PCR products of the desired size were purified by agarose gel electrophoresis followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions. The luciferase ORF and the bsd expression cassette were spliced together to generate a 2.2 kBp stuffer fragment using splice overlap extension PCR (Horton, R.M., Hunt, H.D., Ho, S.N., Pullen, J.K. and Pease, L.R. (1989)). Engineering hybrid genes without the use of restriction enzymes: gene splicing by overlap extension. Gene 77, 61-68) and the primers 5'- CAT CAA GCT TGG CCG GCC ACC ATG GAC GCG TCC GAA GAC GCC AAA AAC ATA AAG -3' (SEQ ID NO:97) and 5'- CAT CAG ATC TGT CGA CCG GAC CGA CGC GTC CAC GAA GTG CTT AGC -3' (SEQ ID NO:98). The resultant SOE PCR product was purified away from the proteins, primers, and salts using a Qiagen PCR clean up kit and following manufacturer's instructions. The product was digested with HinD III and Sal I restriction endonucleases, the restricted product was purified by agarose gel electrophoresis followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions, and the purified DNA was subcloned between the HinD III (NEB, #R0104S) and Xho I (NEB, #R0146S) sites of plasmid pBluescript to yield pBSlucSOEK. Plasmid pBSlucSOEK was sequenced to confirm it was free of unwanted mutations, and the stuffer fragment recovered from the pBSlucSOEK as a HinD III and Rsr II fragment, which was purified by agarose gel electrophoresis, followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions and subcloning of the fragment into the HinD III and Rsr II sites of plasmid pBS3.3'P12 to yield plasmid

pBS33P2lucSOEK. Plasmid V87 was then constructed by recovering from plasmid pBS33P2lucSOEK the luciferase-E7-bsd stuffer fragment along with the 3' flanking sequences as an Fse I – Not I flanked 2.2 kBp DNA product, which was purified by agarose gel electrophoresis followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions. This 2.2 kBp DNA was subcloned between the Fse I and Not I site of plasmid p610-E54P1, to yield vector V87. A schematic drawing of the construction of V87 is shown in Figure 2.

The downstream Mlu I site was removed from V87 by PCR amplification of the stuffer fragment of V90,a derivative of V87 containing the same stuffer as V87, using 1 ng of V90 template DNA and 2.5 µL of primer 5'- CAT CAA GCT TGG CCG GCC ACG CGT GTT GGT AAA ATG GAA GAC G -3' (SEQ ID NO:99) and 2.5 µL of primer 5'- CAT GAG ATC TGT CGA CCG GAC CGC CAC GAA GTG CTT AAG C -3' (SEQ ID NO:100) in a standard 50 µL PCR reaction using Taq DNA polymerase (Roche, 1146165). Cycling parameters were: 94°C for 3 min.; followed by 30 cycles of 94°C for 20 sec., 55°C for 20 sec., and 72°C for 3 minutes; followed by 72°C for 10 minutes; followed by a 4°C soak. The resultant 2.2 kBp PCR product was purified from the proteins and salt using a Qiagen PCR clean up kit following manufacturer's instructions. The PCR product was digested with Fse I and Rsr II endonucleases, purified by agarose gel electrophoresis, and recovered from the gel using a Qiagen Gel Extraction kit according to manufacturer's instructions. The restricted and purified fragment was then subcloned into the Fse I and Rsr II sites of V86, a vector related to V87 but containing a stuffer fragment containing the luciferase ORF but not the bsd ORF, to yield V94. The MCS GSE cassette was recovered from V94 as a 2.2 kBp DNA fragment by digestion of V94 with Bgl II (NEB, #R0144S) and Not I (NEB, #R0189S) restriction endonucleases. Vector V98 was created by subcloning this 2.2 kBp DNA fragment from V94 into the Bgl II and Not I sites on the V97 backbone. A schematic of the construction of V98 is shown in Figure 3.

**2. <u>Random Fragment Library Construction</u>**

For construction of the starting AOLC1U library, V98 vector described above was restricted at 37°C for 3 hours, using Mlu I (NEB, #R0198S) and Rsr II restriction endonucleases. For construction of all other selected libraries, *e.g.*, AOLC1A, AOLC1B, AOLC1C, V98 vector DNA was restricted at 37°C for 3 hours, using Fse I and Rsr II restriction endonucleases. The vector DNA was purified from the digest using a Qiagen

PCR clean up spin column according to manufacturer's instructions, and the vector backbone DNA was purified by subjecting the eluate from the column to agarose gel electrophoresis to resolve the various DNA digestion products according to mass. A gel slice containing the 7.7 kBp backbone fragment was excised, and the DNA recovered from the agarose slice using the Qiagen Gel Extraction kit according to manufacturer's instructions. The concentration of DNA present in the vector preparations was determined by ethidium bromide staining in an 0.8% agarose gel following electrophoresis, by comparison to a DNA sample composed of various bands of known size and mass (High DNA Mass Ladder, Life Technologies, 10406-016). Vector preparations were quality controlled in series of test ligations as follows: vector alone control reaction, composed of x μL vector DNA (30 fmol), z μL water, 4 μL 5X ligase buffer, 1 μL T4 DNA ligase (BRL, 5 U/μL, #15224-041), where x + z = 15 μL; and a vector + insert reaction, composed of x μL vector DNA (30 fmol), y μL insert DNA (90 fmol), z μL water, 4 μL 5X ligase buffer, 1 μL T4 DNA ligase, where x +y + z = 15 μL. Ligation reactions were incubated at 16°C for at least 16 hours. At the end of the incubation period, ligation products were precipitated under ethanol, the ethanol decanted and the precipitate washed three times with 70% EtOH, and the pellet dried and resuspended in 20 μL of water. One microliter of resuspended DNA solution was electrotransformed into DH10B electrocompetent cells (Life Technologies, 18290-015) according to manufacturers instructions. Following transformation, bacteria was recovered in 960 μL of room temperature SOC media, and recovery mixtures incubated at 37°C in a rotary shaker, 250-300 rpm, for at least 40 minutes. After the recovery period, 4 ten-fold serial dilutions of each transformation culture were created, *i.e.*, 1:10, 1:100, 1:1000, and 1:10000, and 50 μL of each bacterial dilution mixture was plated on LB-agar plates containing carbenicillin. Plates were incubated at 37°C overnight, and scored the following morning. Stock solutions of the double-restricted vector were aliquoted and stored frozen at -20°C, preferably in 30 fmol / tube amounts.

3. **Preparation of Randomly fragmented cDNAs from Cell Line mRNA**

Total RNA was harvested from five colon cancer cell lines: HCT15, HT29, HCT116, SW480 and SW620, using a Qiagen RNeasy kit, according to manufacturer's instructions. Poly A+ mRNA was purified from the total RNA using an Oligotex kit (Qiagen) following manufacturer's instructions. The purified mRNA pools were fragmented by boiling the sample at 100° C for 8 minutes, a time empirically determined

to give a good distribution of cDNA fragments as demonstrated using a published fragmentation protocol (Gudkov and Roninson, "Isolation of Genetic Suppressor Elements (GSEs) from Random Fragment cDNA libraries in Retroviral Vectors," Chapter 18, in *Methods in Molecular Biology, Vol. 69: cDNA Library Protocols*, p. 228, I.G. Cowell and C. A. Austin, eds. Humana Press Inc., Totowa NJ, 1997).Two parallel first strand cDNA synthesis reactions were performed using the fragmented mRNAs as template, with either an Asc I-$N_9$ random primer 5'- GTA ATA CGA CTC ACT ATA **GGC GCG CC**$N_9$ -3' (SEQ ID NO:101) or an Rsr II-N9 random primer 5'- GTA ATA CGA CTC ACT ATA GG**C GGA CCG** $N_9$ -3' (SEQ ID NO:102) and the SuperScript Choice Systems for cDNA synthesis (Gibco BRL) following manufacturer's instructions. Second strand synthesis was performed using the method of Gubler and Hoffman Gene 25:263-9, 1989) again using the SuperScript kit. The resultant double strand cDNAs were blunted using T4 DNA polymerase (NEB, #M0203S), then ligated to double stranded adapters, produced by annealing the oligonucleotides 5'- ATG ATT ACG CCA **CGG ACC GTC** -3' (SEQ ID NO:103) and 5'- **GAC GGT CCG** TGG CGT AAT CAT GGT CAT AGC -3' (SEQ ID NO:104) to yield adapters containing an Rsr II restriction site, or the oligonucleotides 5'- ATG ATT ACG CCA **GGC GCG CCA** C -3' (SEQ ID NO:105) and 5'- **GTG GCG CGC** CTG GCG TAA TCA TGG TCA TAG C -3' (SEQ ID NO:106) to yield adapters containing an Asc I restriction site. cDNA samples prepared using the Asc-$N_9$ primer were ligated to the adapters containing the Rsr II restriction site, while cDNA samples prepared using the Rsr II-$N_9$ primer were ligated to adapters containing the Asc I restriction site. After ligation of the adapters to the cDNA fragments, excess adapters were removed by spun column chromatography.

**4. Preparation of Normalized Inserts for Starting AOLC1U Library**

Eluted cDNAs ligated to appropriate adapters were subjected to 22 cycles of PCR to amplify the inserts and to generate large quantities of insert for self-normalization: those inserts ligated to Rsr II adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA CGG ACC GTC -3' (SEQ ID NO:107) and 5'- GTA ATA CGA CTC ACT ATA GGC -3' (SEQ ID NO:108), while inserts ligated to the Asc I adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA GGC GCG CCA C -3' (SEQ ID NO:109) and 5'- GTA ATA CGA CTC ACT ATA GGC GGA C -3' (SEQ ID NO:110). PCR products were pooled, purified using a Qiagen PCR

kit following manufacturer's instructions, evaporated to dryness using a rotary evaporator, and then resuspended in 25 μL of 10 mM Tris-HCl (pH 8.5). The cDNA fragments were normalized by self-hybridization and batch binding hydroxyapatite (HAP) chromatography, essentially as described by Gudkov and Roninson (*op.cit*)., except that samples were collected at 24, 48, 72, 96 hours. The extent of normalization was evaluated using real-time PCR at five loci: ACTB, TP53, CASP3, 18S and a mitochondrial locus.

Purified, normalized ssDNA fractions from the HAP columns were reconverted to dsDNA and amplified using PCR: again, those inserts ligated to Rsr II adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA CGG ACC GTC -3' (SEQ ID NO:111) and 5'- GTA ATA CGA CTC ACT ATA GGC -3' (SEQ ID NO:112), while inserts ligated to the Asc I adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA GGC GCG CCA C -3' (SEQ ID NO:113) and 5'- GTA ATA CGA CTC ACT ATA GGC GGA C -3' (SEQ ID NO:114). PCR products were purified using Qiagen PCR clean up columns following manufacturer's instructions, and the PCR products from the two types of inserts (e.g, those with Rsr II adapters and those with Asc adapters) were mixed one-to-one molar ratio. Approximately 100 ng of mixed PCR product was digested with Asc I (NEB, #R0558S) and Rsr II restriction endonucleases for 2 hours at 37°C in multiple parallel reactions. DNA was recovered from the pooled digestions using a Qiagen PCR clean up kit following manufacturer's instructions. The concentration of restricted PCR products in the eluate was determined by resolving the DNA present in an aliquot of the eluate by 2% agarose gel electrophoresis. The fluorescent intensity of the PCR product band was compared to the intensity of bands in a DNA sample composed of a mixture of DNA fragments of known size and mass (Low DNA Mass Ladder, Life Technologies, 10068-013).

**5. Isolation of GSEs for AOLC1A, AOLC1B, or AOLC1C Libraries.**

Colon adenocarcinoma SW480 cells were engineered to stably express ecotropic retroviral receptor (EcoR), and the resulting cell line was termed SW480 E. Phoenix Eco retrovirus packaging cells were transfected with library plasmid DNA and SW480 E cells were transduced with viral supernatant harvested from the packaging cells. Floating SW480 E cells were collected at times 24, 48, 72 and 96 hours post-transduction and fixed with 100% methanol. Apoptotic cells were collected from all time points by

staining the fixed cells with a monoclonal antibody against caspase-cleaved cytokeratin 18 (M30 CytoDeath Antibody, Roche Diagnostics), and selecting stained cells by fluorescence activated cell sorting (FACS). Genomic DNA was isolated from the collected cells (typically between 1 x $10^5$ and 2 x $10^6$ cells, depending upon the selection round) using the Qiagen DNeasy kit (Qiagen). Recovered genomic DNA was quantitated using the PicoGreen DNA quantitation kit (Molecular Probes) in a fluorometric assay performed according to manufacturer's instructions.

GSEs were recovered from the integrated proviruses contained in the harvested genomic DNA using PCR and the following reaction recipe: 10 μL genomic DNA solution, about 1 μg DNA, 5 μL of 3.3 μM p5x primer 5'- TCT GCA GCC CAG GTA AAA TTC GCT AGC CTC TAG T -3' (SEQ ID NO:115), 5 μL of 3.3 μM p6x primer 5'- GAG GAA CAA GGA AAG CTG AAT ACA CGA CCC GTG AT -3' (SEQ ID NO:116), 2 μL of 10 mM dNTP mix, 17 μL of $H_2O$, 10 μL 5X PCR buffer, 1 μL of Thermozyme (InVitrogen E120-01). Cycling conditions for the PCR were: 95°C for 3 min.; followed by 30 cycles of 95°C for 30 sec., 68°C for 30 sec., 72°C for 1 min.; followed by 72°C for 10 min., followed by a soak at 4°C. At least 10, and typically 96 reactions were performed in parallel.

Two hundred μL of pooled PCR product from the genomic PCR samples was purified from proteins and salts using a Qiagen PCR clean up kit following manufacturer's instructions. The concentration of PCR product in the eluate was determined by resolving the DNA present in an aliquot of the eluate by 2% agarose gel electrophoresis and then comparing the fluorescent intensity of the PCR product band to the intensity of bands in a DNA sample composed of a mixture of DNA fragments of known size and mass (Low DNA Mass Ladder, Life Technologies, 10068-013). Multiple parallel restriction digests were then set up using samples of the purified PCR product present in the eluate using the following recipe: 10 μL 10X NEB buffer #4 (final 1X concentration: 20 mM Tris-acetate, 10 mM magnesium acetate, 50 mM potassium acetate, 1 mM dithiothreitol), 1 μL 100X BSA (NEB), 7 μL Fse I restriction endonuclase (2 U/μL, NEB #R0588S), 3 μL Rsr II restriction endonuclease (4 U/μL, NEB #R0501S), X μL aliquot of PCR product, about 100 ng, 79 μL water, to bring total digestion volume up to 100 μL. Restriction digests were incubated at 37°C for 3 hours. DNA products from the digest were separated from proteins and salts and concentrated using a Zymo DNA Clean & Concentrator-5 concentrator kit (#D4004), following the manufacturer's

instructions with the following modifications: after addition of DNA binding buffer to each of the digestion reactions, all of the reactions were spun through the same column to concentrate 600 to 800 ng of digested insert onto a single column. Columns were washed according to the manufacturer's protocols, and the DNA eluted from the column by two sequential additions of 8 µL of 50 mM Tris-HCl, pH 8.5. DNA of desired sizes (100-500 bp) was recovered from the concentrated eluate by purification using gel electrophoresis on 1% low melting point agarose (NuSieve GTG agarose, FMC bioproducts) gels. DNA bands in the gel were visualized following ethidium bromide staining of the gel, using a hand-held shortwave ultraviolet light source. Gel slices containing the desired DNA were excised using clean razor blades, and DNA extracted from the gel slice using the Qiagen gel purification kit, following manufacturer's instructions. The concentration of restricted and purified PCR product was determined by ethidium bromide staining of an agarose gel containing an aliquot of the purified PCR product, and a DNA sample of known composition and mass, as described above.

5. **cDNA Library Preparation**

Ligation reactions for each batch of insert prepared were set up as follows: (reaction 1) Vector control reaction: x µL vector DNA (150 ng), z µL water, 4 µL 5X ligase buffer, 1 µL T4 DNA ligase (BRL, 5 U/µL, #15224-041), where x + z = 15 µL; (reaction 2) Vector + insert: x µL vector DNA (150 ng), y µL insert DNA (12 ng); z µL water; 4 µL 5X ligase buffer; 1 µL T4 DNA ligase, where x + y + z = 15 µL. Ligation mixtures were incubated at 4°C for at least 16 hours. At the end of the ligation period, ligation products were precipitated under ethanol, the ethanol decanted and the precipitate washed three times with 70% EtOH, and the pellet dried and resuspended in 20 µL of water. One µL of resuspended ligation product was used to electrotransform DH10B electrocompetent cells (Life Technologies, 18290-015) according to manufacturers instructions; the balance of the ligation mixture was stored at –20°C. Following transformation, bacteria was recovered in 960 µL of room temperature SOC media, and recovery mixtures incubated at 37°C in a rotary shaker, 250-300 rpm, for at least 40 minutes. After the recovery period, 4 ten-fold serially diluted samples (*i.e.*, 1:10, 1:100, 1:1000, and 1:10000) of each transformation culture were set up, and 50 µL from each dilution was plated on LB-agar plates containing carbenicillin. Plates were incubated at 37°C overnight, and colony counts for each plate scored the following morning.

Insert sizes in a subset of clones were determined by performing PCR directly on bacterial colonies as follows. A disposable pipette tip was used to harvest a single bacterial colony from the LB plate of interest. The colony was transferred into 25 µL of water, carefully swishing the tip to dislodge the bacterial colony. Five microliters of bacterial solution was spotted to an LB plate and allowed to incubate overnight. PCR was performed on the bacterial solution using the following recipe: 2 µL 10 mM primer M13F(17) 5'- GTA AAA CGA CGG CCA GT -3' (SEQ ID NO:117), 2 µL 10 mM primer p6X 5'- TCT GCA GCC CAG GTA AAA TTC GCT AGC CTC TAG T -3' (SEQ ID NO:118), 4 µL 10X PCR buffer, 1 µL 25 mM dNTP mix, 0.5 µL Taq DNA polymerase (Roche, 1146165), 10.5 µL PCR grade water, 20 µL of bacterial solution. The cycling parameters were 95°C for 3 min., then 25 cycles of 95°C for 30 sec., 60°C for 30 sec., 72°C for 1 min., followed by 72°C for 5 min., and a 4°C soak. At the completion of the PCR, 10 µL of each PCR product was resolved on a 2% agarose gel containing ethidium bromide. DNA mobility for each of the samples was evaluated. The balance of the PCR product was submitted for DNA sequencing to determine the sequence content of the inserts for these clones.

Ligations described above were used for further electro-transformations. The calculated cfu / µg for each of the QC controlled ligations was used to compute the total number of electrotransformations required to achieve the required complexity for the library being constructed. Multiple electrotransformations were performed in parallel, using 1 µL of ligation mix per transformation as described above. At the end of the 40-minute recovery period following the electrotransformation, up to 10 independent transformations were pooled, and 50 µL from these pooled samples used to establish 4 ten-fold serially diluted samples (*i.e.*, 1:10, 1:100, 1:1000, and 1:10000). Fifty µL of each serial dilution (*i.e.*, 1:10, 1:100, 1:1000, and 1:10000) was plated on LB-agar plates containing carbenicillin. The remaining volumes of undiluted and diluted transformation solutions were used to seed a bacterial culture flask containing 0.5L of LB broth, after which the seeded flask was incubated at 30°C overnight, about 14 – 16 hours, in a rotary shaker at 300 rpm. Plates from the serially diluted samples were incubated at 37°C overnight, and colony counts for each plate scored the following morning to determine the total number of colonies seeded into the 0.5L culture. Library plasmid DNA was recovered from the 0.5L cultures using a Qiagen Maxiprep plasmid kit, according to manufacturer's instructions.

The AOLC1U library was constructed using the normalized inserts prepared as described in section 4 above; the library was composed of greater than 80 million transformants. The AOLC1A library was constructed from GSEs recovered from apoptotic HCT116 cells collected 24, 48, 72 and 96 hours after transduction. The AOLC1B library was constructed from GSEs recovered from apoptotic HCT116 cells collected 24, 48, and 72 hours after transduction. The AOLC1C library was constructed from GSEs recovered from apoptotic HCT116 cells collected 48 hours after transduction. It was found that the AOLC1C library was highly enriched for RPX and *E. coli* sequences; with the RPL5, RPL36, RPL8, Fau, RPL13a species being the majority species. To subtract these sequences from AOLC1C library, the following procedure was performed: (1) library DNA was linearized using FseI restriction endonuclease, (2) primers specific to selected RPX and *E. coli* species were annealed to linearized DNA and (3) DNA synthesis extended from the primer using Bst DNA polymerase, a polymerase that lacks 3' exonuclease activity. Upon primer extension, the overhang of the FseI half-site adjacent to the insert will be lost, since extension products will yield blunt dsDNA. This blunted Fse I half-site will be incapable of adhering to the cohesive Fse I half-site present at the other end of the plasmid. Therefore, the DNA molecules to which primers have bound (*e.g.* the RPX and *E. coli* species) should have their Fse I sites blunted, and therefore be incapable of resealing by T4 DNA ligase. Hence, all linearized library DNA is treated with T4 DNA ligase, and the ligation products are transformed into electocompetent DH10B *E.coli* to generate a library enriched in sequences that do not contain RPX or *E coli* species. The enriched or subtracted library so created from the AOLC1C library was termed AOLC1CS. Sequencing of the AOLC1CS library showed that the targeted plasmids were substantially reduced in number, but they were still predominant species in the AOLC1CS library. Thus, the AOLC1CS library was subjected to another round of subtraction using the same method, with the resulting library termed AOLC1CS2 (AOLC1C library after 2 rounds of subtraction). The primers used in this method to make library AOLC1CS were: RPS5: 5'- TCG TTC GAG GAG CCC TTG GCA GCA T -3' (SEQ ID NO:119); RPL36A, 5'- CGC CCT TCC GCC ACG GCC GTC TCT -3' (SEQ ID NO:120); RPL18 5'- GAA AGG ACC CGT CGC CAT GGG CCG T -3' (SEQ ID NO:121); Fau, 5'- CAG TCG CCA ATA TGC AGC TCT TTG T -3' (SEQ ID NO:122); RPL13A , 5'- CGA GGT ATG CTG CCC CAC AA -3' (SEQ ID NO:123). For library AOLC1CS2, the above primers were used and these primers were

added as well: RPS5, 5'- CGA GCG CCT GTG CAC AGC AGC CAG A -3' (SEQ ID NO:124); RPL36A, 5'- GCG GGA CAT GAT TCG GGA GGT GTG T -3' (SEQ ID NO:125); RPL8, 5'- CTG CGC GCC TGC GCG CCG TGG ATT T -3' (SEQ ID NO:126); Fau, 5'- CTT CGA GGT GAC CGG CCA GGA AAC G -3' (SEQ ID NO:127); RPL13A, 5'- CAG GCC GCT CTG GAC CGT CTC AAG G -3' (SEQ ID NO:128); *E coli*, 5'- AAC GGT GGG CTT GTT GCT GCT CTG G -3' (SEQ ID NO:129), 5'- ATT GGT ATT GGT AAC GGG CGT CAG G -3' (SEQ ID NO:130), 5'- ACC ATC TTC CAG GCG CAG TTG AGT T -3' (SEQ ID NO:131).

The target genes and encoded proteins identified by the present invention are explicitly disclosed in Table 1, which contains a common name for the gene and the GENBANK accession number, which can be retrieved from public sequence databases, as well as a sequence identifier for the nucleic acid sequence (first number) and encoded amino acid sequence (second number).

**Table 1**

| Accession Number | Common Name | Sequence Identifier (nucleic acid & protein) | Description |
|---|---|---|---|
| NM_001087 | AAMP | SEQ ID NO:1 & 2 | angio-associated, migratory cell protein |
| NM_001109 | ADAM8 | SEQ ID NO:3 & 4 | a disintegrin and metalloproteinase domain 8 |
| NM_139057 | ADAMTS17 | SEQ ID NO:5 & 6 | a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 17 |
| NM_004036 | ADCY3 | SEQ ID NO:7 & 8 | adenylate cyclase 3 |
| NM_001619 | ADRBK1 | SEQ ID NO:9 & 10 | adrenergic, beta, receptor kinase 1 |
| NM_006698 | BLCAP | SEQ ID NO:11 & 12 | bladder cancer associated protein |
| NM_012264 | C22orf5 | SEQ ID NO:13 & 14 | chromosome 22 open reading frame 5 |
| NM_004356 | CD81 | SEQ ID NO:15 & 16 | CD81 antigen (target of antiproliferative antibody 1) |
| NM_001769 | CD9 | SEQ ID NO:17 & 18 | CD9 antigen (p24) |
| NM_001305 | CLDN4 | SEQ ID NO:19 & 20 | claudin 4 |
| NM_001288 | CLIC1 | SEQ ID NO:21 & 22 | chloride intracellular channel 1 |
| NM_058175 | COL6A2 | SEQ ID NO:23 & 24 | collagen, type VI, alpha 2 |
| AF070636 or NM_020428 | CTL2 | SEQ ID NO:25 & 26 | CTL2 gene |
| NM_001397 | ECE1 | SEQ ID NO:27 & 28 | endothelin converting enzyme 1 |
| NM_004429 | EFNB1 | SEQ ID NO:29 & 30 | ephrin-B1 |
| NM_004475 | FLOT2 | SEQ ID NO:31 & 32 | flotillin 2 |
| AC011511 or BC058903 | ICAM3 | SEQ ID NO:33 & 34 | intercellular adhesion molecule 3 |

| Accession Number | Common Name | Sequence Identifier (nucleic acid & protein) | Description |
|---|---|---|---|
| NM_006123 | IDS | SEQ ID NO:35 & 36 | iduronate 2-sulfatase (Hunter syndrome) |
| NM_002226 | JAG2 | SEQ ID NO:37 & 38 | jagged 2 |
| BC001699 | JAM1 | SEQ ID NO:39 & 40 | junctional adhesion molecule 1 |
| NM_005567 | LGALS3BP | SEQ ID NO:41 & 42 | lectin, galactoside-binding, soluble, 3 binding protein |
| XM_085426 | LOC146330 | SEQ ID NO:43 & 44 | similar to possible G-protein receptor |
| BC020590 | LOC51107 | SEQ ID NO:45 & 46 | CGI-78 protein |
| NM_000237 | LPL | SEQ ID NO:47 & 48 | lipoprotein lipase |
| NM_002335 | LRP5 | SEQ ID NO:49 & 50 | low density lipoprotein receptor-related protein 5 |
| NM_005581 | LU | SEQ ID NO:51 & 52 | Lutheran blood group (Auberger b antigen included) |
| NM_005898 | M11S1 | SEQ ID NO:53 & 54 | membrane component, chromosome 11, surface marker 1 |
| NM_007061 | MSE55 | SEQ ID NO:55 & 56 | serum constituent protein |
| NM_006702 | NTE | SEQ ID NO:57 & 58 | neuropathy target esterase |
| AK055605 or AK126101 | PLXNA1 | SEQ ID NO:59 & 60 | Homo sapiens cDNA FLJ31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 |
| AF034800 | PPFIA3 | SEQ ID NO:61 & 62 | protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 3 |
| NM_145648 | PTR4 | SEQ ID NO:63 & 64 | Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA |
| NM_004207 | SLC16A3 | SEQ ID NO:65 & 66 | solute carrier family 16 (monocarboxylic acid transporters), member 3 |
| NM_005628 | SLC1A5 | SEQ ID NO:67 & 68 | solute carrier family 1 (neutral amino acid transporter), member 5 |
| NM_014437 | SLC39A1 | SEQ ID NO:69 & 70 | solute carrier family 39 (zinc transporter), member 3 |
| NM_021102 | SPINT2 | SEQ ID NO:71 & 72 | serine protease inhibitor, Kunitz type, 2 |
| NM_003714 | STC2 | SEQ ID NO:73 & 74 | stanniocalcin 2 |
| NM_014452 | TNFRSF21 | SEQ ID NO:75 & 76 | tumor necrosis factor receptor superfamily, member 21 |
| NM_003299 | TRA1 | SEQ ID NO:77 & 78 | tumor rejection antigen (gp96) 1 |
| NM_017636 | TRPM4 | SEQ ID NO:79 & 80 | transient receptor potential cation channel, subfamily M, member 4 |

It should be understood that the foregoing disclosure emphasizes certain specific embodiments of the invention and that all modifications or alternatives equivalent thereto are within the spirit and scope of the invention as set forth in the appended claims.

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**WHAT WE CLAIM IS:**

1. A method for identifying a compound for inducing apoptosis, comprising identifying an inhibitor of a target selected from the group consisting of: angio-associated, migratory cell protein (AAMP, comprising SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8, comprising SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17, comprising SEQ ID NO:6),, adenylate cyclase 3 (ADCY3, comprising SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1, comprising SEQ ID NO:10), bladder cancer associated protein (BLCAP, comprising SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5, comprising SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81, comprising SEQ ID NO:16), CD9 antigen (p24) (CD9, comprising SEQ ID NO:18), claudin 4 (CLDN4, comprising SEQ ID NO:20), chloride intracellular channel 1 (CLIC1, comprising SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2, comprising SEQ ID NO:24), CTL2 (CTL2, comprising SEQ ID NO:26), endothelin converting enzyme 1 (ECE1, comprising SEQ ID NO:28), ephrin-B1 (EFNB1, comprising SEQ ID NO:30), flotillin 2 (FLOT2, comprising SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3, comprising SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS, comprising SEQ ID NO:36), jagged 2 (JAG2, comprising SEQ ID NO:38), junctional adhesion molecule 1 (JAM1, comprising SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP, comprising SEQ ID NO:42), similar to possible G-protein receptor (LOC146330, comprising SEQ ID NO:44), CGI-78 protein (LOC51107, comprising SEQ ID NO:46), lipoprotein lipase (LPL, comprising SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5, comprising SEQ ID NO:50), Lutheran blood group (Auberger b antigen included) (LU, comprising SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1, comprising SEQ ID NO:54), serum constituent protein (MSE55, comprising SEQ ID NO:56), neuropathy target esterase (NTE, comprising SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1, comprising SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein )(liprin), alpha 3 (PPFIA3, comprising SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4, comprising SEQ ID NO:64), solute carrier family 16

(moncarboxylic acid transporters) member 3 (SLC16A3, comprising SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5, comprising SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1, comprising SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2, comprising SEQ ID NO:72), stanniocalcin 2 (STC2, comprising SEQ ID NO:74), tumor necrosis receptor superfamily member 21 (TNFRSF21, comprising SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1, comprising SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4, comprising SEQ ID NO:80).

2. The method of Claim 1, further comprising assessing the ability of an identified inhibitor to induce apoptosis in a cell.

3. The method of Claim 2, further comprising detecting whether a compound identified as inducing apoptosis inhibits growth of tumor cells.

4. The method of Claim 1, wherein the step of identifying comprises identifying an inhibitor of expression or activity of the target.

5. The method of Claim 1, comprising the steps of:

a) contacting a host cell with a putative regulatory compound, wherein the host cell expresses the target or a biologically active fragment thereof; and

b) detecting whether the putative regulatory compound inhibits the target or biologically active fragment thereof, wherein a putative regulatory compound that inhibits the target as compared to in the absence of the compound is indicated to be a candidate compound for the induction of apoptosis in a host cell.

6. The method of Claim 5, wherein the host cell is a tumor cell line.

7. The method of Claim 5, wherein the step of detecting is selected from the group consisting of:

a) detecting expression of the target in the presence of the putative regulatory compound; and

b) detecting activity of the target in the presence of the putative regulatory compound.

8. The method of Claim 7, wherein the expression of the target is measured by polymerase chain reaction.

9. The method of Claim 7, wherein the expression of the target is measured using an antibody or antigen binding partner that selectively binds to the target.

10. The method of Claim 7, wherein the activity of the target is measured by measuring the amount of a product generated in a biochemical reaction mediated by the target.

11. The method of Claim 7, wherein the activity of the target is measured by measuring the amount of a substrate consumed in a biochemical reaction mediated by the target.

12. The method of Claim 1, comprising the steps of:

a) determining the three-dimensional structure of the target;

b) identifying the three-dimensional structure of a putative inhibitor by using computer software to model an interaction between the target structure and a structure of a test compound; and

c) synthesizing compounds identified in (b) and assaying the compounds in an *in vitro* assay to determine whether the compound inhibits the expression or activity of the target.

13. The method of Claim 1, wherein the target has been validated as being involved in tumor cell growth.

14. The method of Claim 14, wherein the target has been validated as being involved in tumor cell growth by a process comprising:

a) inhibiting the target in a cell by a method selected from the group consisting of gene knock-out, anti-sense oligonucleotide expression, use of RNAi molecules and GSE expression; and

b) assaying the cell for the ability of the cell to grow.

15. A method for inducing apoptosis, comprising inhibiting the expression or activity of a target or a gene encoding the target, wherein the target is selected from the group consisting of: angio-associated, migratory cell protein (AAMP, comprising SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8, comprising SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17, comprising SEQ ID NO:6), adenylate cyclase 3 (ADCY3, comprising SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1, comprising SEQ ID NO:10), bladder cancer associated protein (BLCAP, comprising SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5, comprising SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81, comprising SEQ ID NO:16), CD9 antigen (p24) (CD9, comprising SEQ ID NO:18), claudin 4 (CLDN4, comprising SEQ ID

NO:20), chloride intracellular channel 1 (CLIC1, comprising SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2, comprising SEQ ID NO:24), CTL2 (CTL2, comprising SEQ ID NO:26), endothelin converting enzyme 1 (ECE1, comprising SEQ ID NO:28), ephrin-B1 (EFNB1, comprising SEQ ID NO:30), flotillin 2 (FLOT2, comprising SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3, comprising SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS, comprising SEQ ID NO:36), jagged 2 (JAG2, comprising SEQ ID NO:38), junctional adhesion molecule 1 (JAM1, comprising SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP, comprising SEQ ID NO:42), similar to possible G-protein receptor (LOC146330, comprising SEQ ID NO:44), CGI-78 protein (LOC51107, comprising SEQ ID NO:46), lipoprotein lipase (LPL, comprising SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5, comprising SEQ ID NO:50), Lutheran blood group (Auberger b antigen included) (LU, comprising SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1, comprising SEQ ID NO:54), serum constituent protein (MSE55, comprising SEQ ID NO:56), neuropathy target esterase (NTE, comprising SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1, comprising SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein )(liprin), alpha 3 (PPFIA3, comprising SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4, comprising SEQ ID NO:64), solute carrier family 16 (moncarboxylic acid transporters) member 3 (SLC16A3, comprising SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5, comprising SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1, comprising SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2, comprising SEQ ID NO:72), stanniocalcin 2 (STC2, comprising SEQ ID NO:74), tumor necrosis receptor superfamily member 21 (TNFRSF21, comprising SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1, comprising SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4, comprising SEQ ID NO:80).

16. The method of Claim 15, wherein the step of inhibiting is conducted by contacting a cell with an inhibitor of the target, wherein the inhibitor induces apoptosis in the cell.

17. A method for the diagnosis of a tumor comprising:

a) detecting a level of expression or activity of at least one biomarker in a test sample from a patient to be diagnosed, wherein the biomarker is selected from the group consisting of: angio-associated, migratory cell protein (AAMP, comprising SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8, comprising SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17, comprising SEQ ID NO:6), adenylate cyclase 3 (ADCY3, comprising SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1, comprising SEQ ID NO:10), bladder cancer associated protein (BLCAP, comprising SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5, comprising SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81, comprising SEQ ID NO:16), CD9 antigen (p24) (CD9, comprising SEQ ID NO:18), claudin 4 (CLDN4, comprising SEQ ID NO:20), chloride intracellular channel 1 (CLIC1, comprising SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2, comprising SEQ ID NO:24), CTL2 (CTL2, comprising SEQ ID NO:26), endothelin converting enzyme 1 (ECE1, comprising SEQ ID NO:28), ephrin-B1 (EFNB1, comprising SEQ ID NO:30), flotillin 2 (FLOT2, comprising SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3, comprising SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS, comprising SEQ ID NO:36), jagged 2 (JAG2, comprising SEQ ID NO:38), junctional adhesion molecule 1 (JAM1, comprising SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP, comprising SEQ ID NO:42), similar to possible G-protein receptor (LOC146330, comprising SEQ ID NO:44), CGI-78 protein (LOC51107, comprising SEQ ID NO:46), lipoprotein lipase (LPL, comprising SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5, comprising SEQ ID NO:50), Lutheran blood group (Auberger b antigen included) (LU, comprising SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1, comprising SEQ ID NO:54), serum constituent protein (MSE55, comprising SEQ ID NO:56), neuropathy target esterase (NTE, comprising SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1, comprising SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein )(liprin), alpha 3 (PPFIA3, comprising SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4, comprising SEQ ID NO:64), solute carrier family 16

(moncarboxylic acid transporters) member 3 (SLC16A3, comprising SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5, comprising SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1, comprising SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2, comprising SEQ ID NO:72), stanniocalcin 2 (STC2, comprising SEQ ID NO:74), tumor necrosis receptor superfamily member 21 (TNFRSF21, comprising SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1, comprising SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4, comprising SEQ ID NO:80);

b) comparing the level of expression or activity of the biomarker in the test sample to a baseline level of biomarker expression or activity established from a control sample; wherein detection of a statistically significant difference in the expression or activity of the biomarker in the test sample, as compared to the baseline level of the expression or biological activity of the biomarker, is an indicator of a difference in the tumorigenicity or potential therefore of cells in the patient.

18. The method of Claim 17, wherein the step of detecting comprises detecting biomarker mRNA transcription in the test sample.

19. The method of Claim 18, wherein the step of detecting is by a method selected from the group consisting of polymerase chain reaction (PCR), reverse transcriptase-PCR (RT-PCR), *in situ* hybridization, Northern blot, sequence analysis, gene microarray analysis, and detection of a reporter gene.

20. The method of Claim 17, wherein the step of detecting comprises detecting the biomarker protein in the test sample.

21. The method of Claim 20, wherein the step of detecting is by a method selected from the group consisting of immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunohistochemistry and immunofluorescence.

22. The method of Claim 17, wherein the step of detecting comprises detecting biomarker biological activity in the test sample.

23. The method of Claim 17, wherein detection of a statistically significant difference in the level of biomarker expression or activity in the test sample as compared to the baseline level, with a confidence of $p<0.05$, indicates that the cells in the test

sample have a difference in tumorigenicity or potential therefore as compared to the control sample.

24. The method of Claim 17, wherein the test sample is from a patient being diagnosed for cancer and wherein the baseline level is established from a control sample that is established as non-tumorigenic.

25. The method of Claim 24, wherein an increase in the level of biomarker expression or activity of the test sample as compared to the baseline level of expression or activity indicates that cells from which the test sample was derived are predicted to be tumorigenic or predisposed to becoming tumorigenic.

26. The method of Claim 17, wherein the test sample is from a patient who is known to have cancer, and wherein the baseline level comprises a level of biomarker expression or activity from a previous tumor cell sample from the patient;

wherein a statistically significant decrease in the level of biomarker expression or activity in the test sample as compared to the first baseline level of expression or activity from the previous tumor cell sample, indicates that the test sample is less tumorigenic than the previous tumor cell sample;

and wherein a statistically significant increase in the level of biomarker expression or activity in the test sample as compared to the first baseline level of expression or activity, indicates that the test sample is more tumorigenic than the previous tumor cell sample.

27. The method of Claim 26, wherein the method further comprises a step (c) of modifying cancer treatment for the patient based on whether an increase or decrease in tumorigenicity is indicated in step (b).

28. The method of Claim 17, wherein the baseline level is established by a method selected from the group consisting of:

(1) establishing a baseline level of biomarker expression or activity in an autologous control sample from the patient, wherein the autologous sample is from a same cell type, tissue type or bodily fluid type as the test sample of step (a);

(2) establishing a baseline level of biomarker expression or activity from at least one previous detection of biomarker expression or activity in a previous test sample from the patient, wherein the previous test sample was of a same cell type, tissue type or bodily fluid type as the test sample of step (a); and

(3) establishing a baseline level of biomarker expression or activity from an average of control samples of a same cell type, tissue type or bodily fluid type as the test sample of step (a), the control samples having been obtained from a population of matched individuals.

29. The method of Claim 17, wherein the patient test sample is immobilized on a substrate.

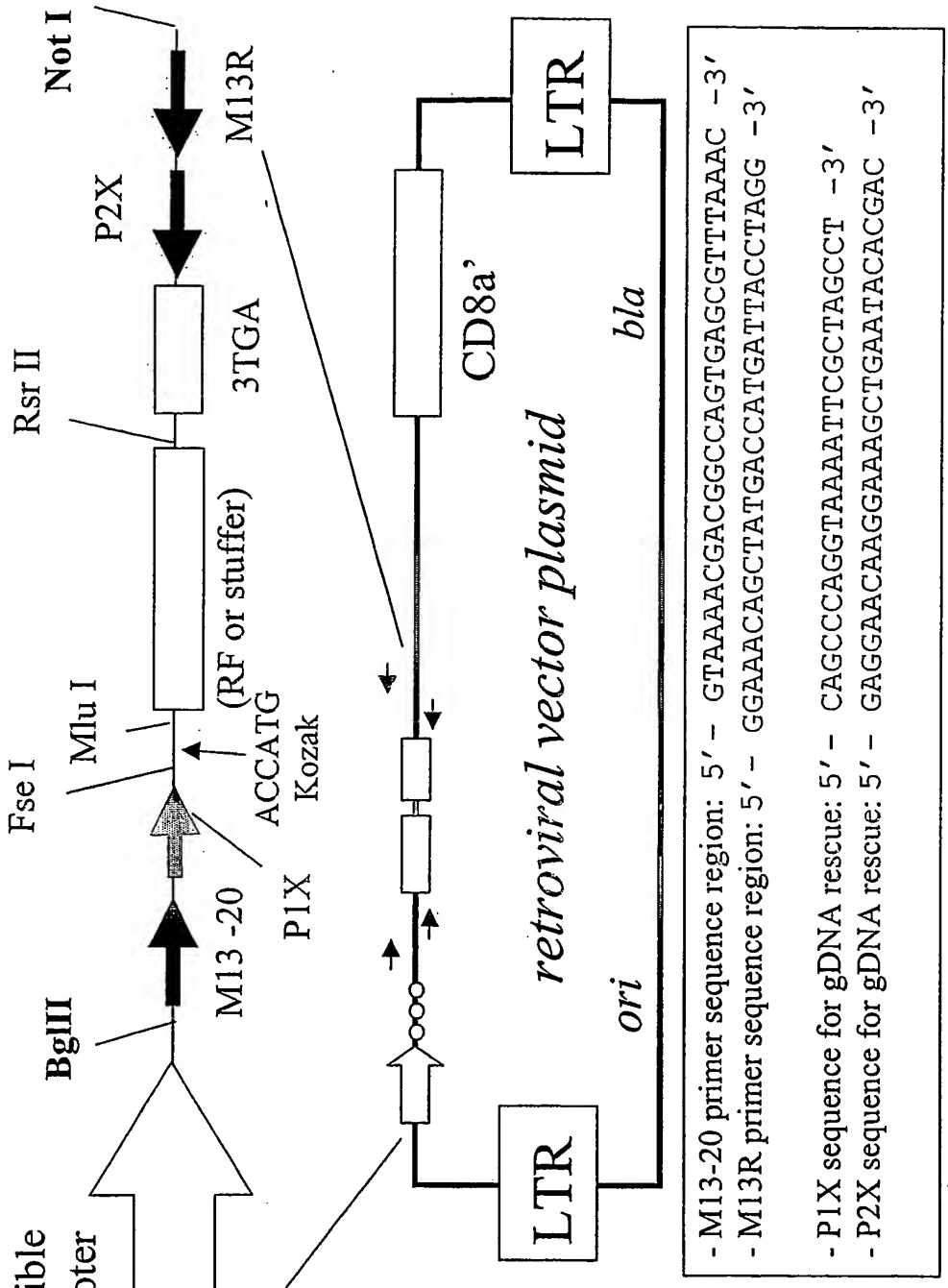
30. The method of Claim 17, wherein the test sample is a bodily fluid sample.

31. The method of Claim 17, wherein the biomarker level is determined by contacting the patient test sample with an antibody or a fragment thereof that selectively binds specifically to the biomarker, and determining whether the antibody or fragment thereof has bound to the marker.

32. The method of Claim 17, wherein the method is used to determine the prognosis for cancer in the patient.

33. The method of Claim 17, wherein the method is used to determine the susceptibility of the patient to a therapeutic treatment.

Fig. 1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M13 -20
P1X
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Mlu I
ACCATG
Kozak
(RF or stuffer)
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P2X
Not I
M13R
LTR
ori
retroviral vector plasmid
bla
CD8a'
LTR
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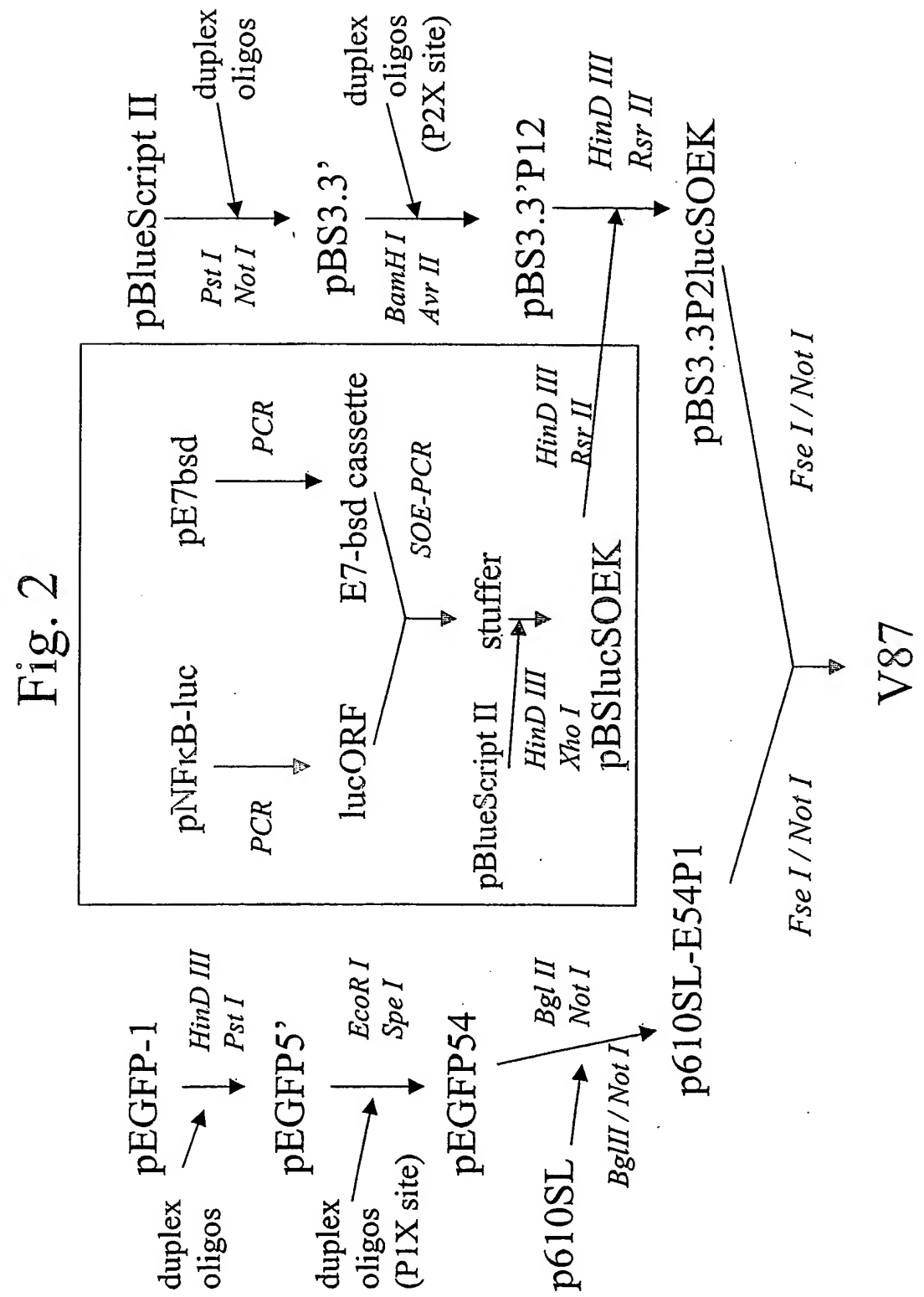
Fig. 2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PCR
lucORF
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PCR
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SOE-PCR
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Xho I
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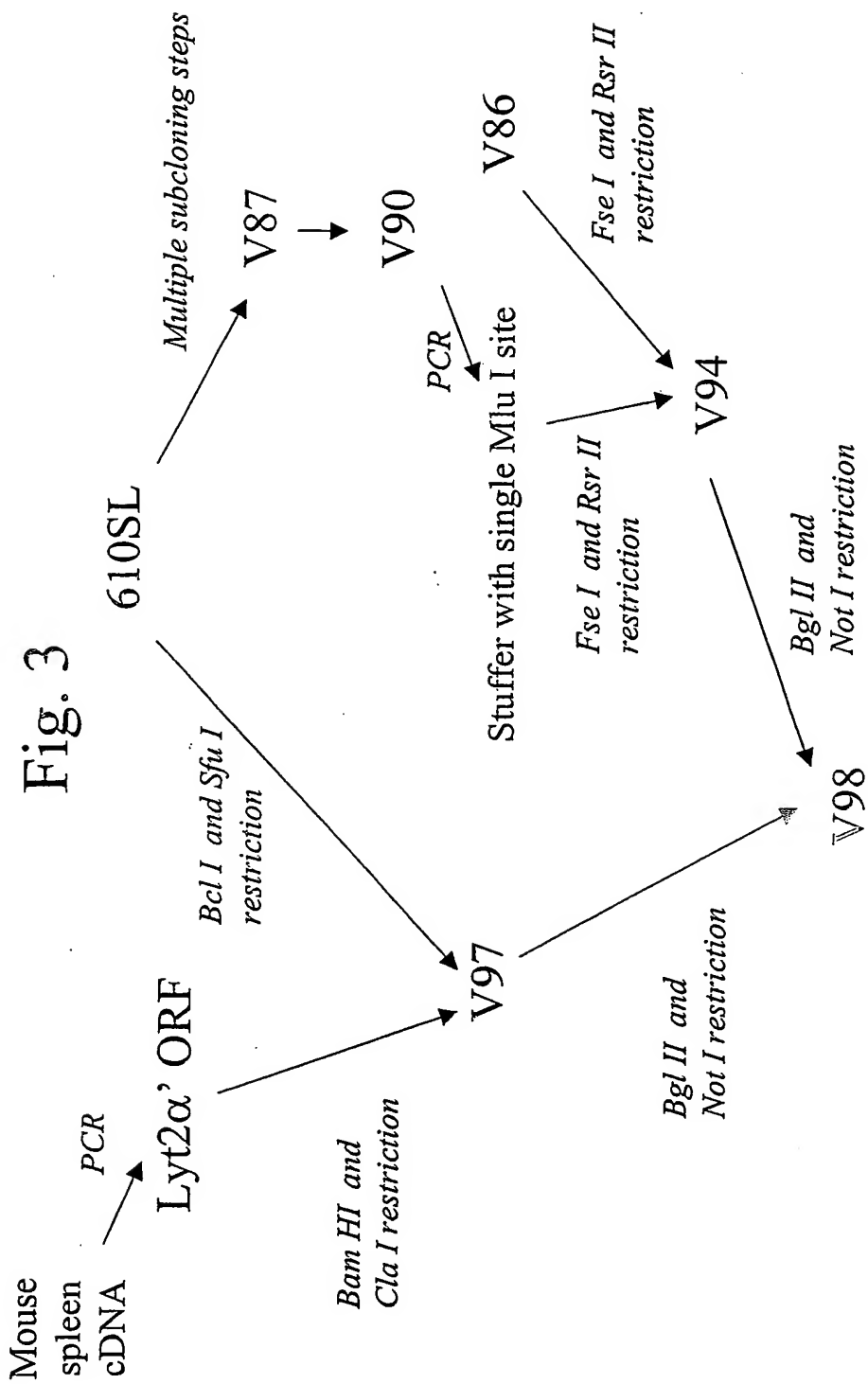
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Bcl I and Sfu I restriction
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PCR
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    800                 805                 810

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Lys Gln Gly Ala Gly Ala Pro Thr Ala Pro
815                 820

ggaaatttgg agaagttgcg gcagagaagc catgcgttcc agccttccac ggtccagcta    2564

gtgccgctca gccctagacc ctgactttgc aggctcagct gctgttctaa cctcagtaat    2624

gcatctacct gagaggctcc tgctgtccac gccctcagcc aattccttct ccccgccttg    2684

gccacgtgta gccccagctg tctgcaggca ccaggctggg atgagctgtg tgcttgcggg    2744

tgcgtgtgtg tgtacgtgtc tccaggtggc cgctggtctc ccgctgtgtt caggaggcca    2804

catatacagc ccctcccagc cacacctgcc cctgctctgg ggcctgctga gccggctgcc    2864

ctgggcaccc ggttccaggc agcacagacg tggggcatcc ccagaaagac tccatcccag    2924

gaccaggttc ccctccgtgc tcttcgagag ggtgtcagtg agcagactgc accccaagct    2984

cccgactcca ggtcccctga tcttgggcct gtttcccatg ggattcaaga gggacagccc    3044

cagctttgtg tgtgtttaag cttaggaatg ccctttatgg aaagggctat gtgggagagt    3104

cagctatctt gtctggtttt cttgagacct cagatgtgtg ttcagcaggg ctgaaagctt    3164

ttattcttta ataatgagaa atgtatattt tactaataaa ttattgaccg agttctgtag    3224

attcttgtta ga                                                       3236
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1               5                   10                  15

Ile Ala Pro Ser Arg Pro Trp Ala Leu Met Glu Gln Tyr Glu Val Val
            20                  25                  30

Leu Pro Arg Arg Leu Pro Gly Pro Arg Val Arg Arg Ala Leu Pro Ser
        35                  40                  45

His Leu Gly Leu His Pro Glu Arg Val Ser Tyr Val Leu Gly Ala Thr
    50                  55                  60

Gly His Asn Phe Thr Leu His Leu Arg Lys Asn Arg Asp Leu Leu Gly
65                  70                  75                  80
```

Ser Gly Tyr Thr Glu Thr Tyr Thr Ala Ala Asn Gly Ser Glu Val Thr
85 90 95

Glu Gln Pro Arg Gly Gln Asp His Cys Leu Tyr Gln Gly His Val Glu
100 105 110

Gly Tyr Pro Asp Ser Ala Ala Ser Leu Ser Thr Cys Ala Gly Leu Arg
115 120 125

Gly Phe Phe Gln Val Gly Ser Asp Leu His Leu Ile Glu Pro Leu Asp
130 135 140

Glu Gly Gly Glu Gly Gly Arg His Ala Val Tyr Gln Ala Glu His Leu
145 150 155 160

Leu Gln Thr Ala Gly Thr Cys Gly Val Ser Asp Asp Ser Leu Gly Ser
165 170 175

Leu Leu Gly Pro Arg Thr Ala Ala Val Phe Arg Pro Arg Pro Gly Asp
180 185 190

Ser Leu Pro Ser Arg Glu Thr Arg Tyr Val Glu Leu Tyr Val Val Val
195 200 205

Asp Asn Ala Glu Phe Gln Met Leu Gly Ser Glu Ala Ala Val Arg His
210 215 220

Arg Val Leu Glu Val Val Asn His Val Asp Lys Leu Tyr Gln Lys Leu
225 230 235 240

Asn Phe Arg Val Val Leu Val Gly Leu Glu Ile Trp Asn Ser Gln Asp
245 250 255

Arg Phe His Val Ser Pro Asp Pro Ser Val Thr Leu Glu Asn Leu Leu
260 265 270

Thr Trp Gln Ala Arg Gln Arg Thr Arg Arg His Leu His Asp Asn Val
275 280 285

Gln Leu Ile Thr Gly Val Asp Phe Thr Gly Thr Thr Val Gly Phe Ala
290 295 300

Arg Val Ser Ala Met Cys Ser His Ser Ser Gly Ala Val Asn Gln Asp
305 310 315 320

His Ser Lys Asn Pro Val Gly Val Ala Cys Thr Met Ala His Glu Met
325 330 335

Gly His Asn Leu Gly Met Asp His Asp Glu Asn Val Gln Gly Cys Arg
340 345 350

Cys Gln Glu Arg Phe Glu Ala Gly Arg Cys Ile Met Ala Gly Ser Ile
355 360 365

Gly Ser Ser Phe Pro Arg Met Phe Ser Asp Cys Ser Gln Ala Tyr Leu
370 375 380

Glu Ser Phe Leu Glu Arg Pro Gln Ser Val Cys Leu Ala Asn Ala Pro
385 390 395 400

Asp Leu Ser His Leu Val Gly Gly Pro Val Cys Gly Asn Leu Phe Val
405 410 415

Glu Arg Gly Glu Gln Cys Asp Cys Gly Pro Pro Glu Asp Cys Arg Asn
420 425 430

Arg Cys Cys Asn Ser Thr Thr Cys Gln Leu Ala Glu Gly Ala Gln Cys
435 440 445

Ala His Gly Thr Cys Cys Gln Glu Cys Lys Val Lys Pro Ala Gly Glu
450 455 460

Leu Cys Arg Pro Lys Lys Asp Met Cys Asp Leu Glu Glu Phe Cys Asp
465 470 475 480

Gly Arg His Pro Glu Cys Pro Glu Asp Ala Phe Gln Glu Asn Gly Thr
485 490 495

Pro Cys Ser Gly Gly Tyr Cys Tyr Asn Gly Ala Cys Pro Thr Leu Ala
500 505 510

Gln Gln Cys Gln Ala Phe Trp Gly Pro Gly Gly Gln Ala Ala Glu Glu
515 520 525

Ser Cys Phe Ser Tyr Asp Ile Leu Pro Gly Cys Lys Ala Ser Arg Tyr
530 535 540

Arg Ala Asp Met Cys Gly Val Leu Gln Cys Lys Gly Gly Gln Gln Pro
545 550 555 560

Leu Gly Arg Ala Ile Cys Ile Val Asp Val Cys His Ala Leu Thr Thr
565 570 575

Glu Asp Gly Thr Ala Tyr Glu Pro Val Pro Glu Gly Thr Arg Cys Gly
580 585 590

Pro Glu Lys Val Cys Trp Lys Gly Arg Cys Gln Asp Leu His Val Tyr
595 600 605

Arg Ser Ser Asn Cys Ser Ala Gln Cys His Asn His Gly Val Cys Asn
610 615 620

His Lys Gln Glu Cys His Cys His Ala Gly Trp Ala Pro Pro His Cys
625 630 635 640

Ala Lys Leu Leu Thr Glu Val His Ala Ala Ser Gly Ser Leu Pro Val
645 650 655

Leu Val Val Val Val Leu Val Leu Leu Ala Val Val Leu Val Thr Leu
660 665 670

Ala Gly Ile Ile Val Tyr Arg Lys Ala Arg Ser Arg Ile Leu Ser Arg
675 680 685

Asn Val Ala Pro Lys Thr Thr Met Gly Arg Ser Asn Pro Leu Phe His
690 695 700

Gln Ala Ala Ser Arg Val Pro Ala Lys Gly Gly Ala Pro Ala Pro Ser
705 710 715 720

```
Arg Gly Pro Gln Glu Leu Val Pro Thr Thr His Pro Gly Gln Pro Ala
                725                 730                 735

Arg His Pro Ala Ser Ser Val Ala Leu Lys Arg Pro Pro Pro Ala Pro
            740                 745                 750

Pro Val Thr Val Ser Ser Pro Pro Phe Pro Val Pro Val Tyr Thr Arg
        755                 760                 765

Gln Ala Pro Lys Gln Val Ile Lys Pro Thr Phe Ala Pro Pro Val Pro
    770                 775                 780

Pro Val Lys Pro Gly Ala Gly Ala Ala Asn Pro Gly Pro Ala Glu Gly
785                 790                 795                 800

Ala Val Gly Pro Lys Val Ala Leu Lys Pro Pro Ile Gln Arg Lys Gln
                805                 810                 815

Gly Ala Gly Ala Pro Thr Ala Pro
            820
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<213> Homo sapiens

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<222> (24)..(3311)
<223>

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                           Met Cys Asp Gly Ala Leu Leu Pro Pro Leu
                           1               5                   10

gtc ctg ccc gtg ctg ctg ctg ctg gtt tgg gga ctg gac ccg ggc aca      101
Val Leu Pro Val Leu Leu Leu Leu Val Trp Gly Leu Asp Pro Gly Thr
                15                  20                  25

gct gtc ggc gac gcg gcg gcc gac gtg gag gtg gtg ctc ccg tgg cgg      149
Ala Val Gly Asp Ala Ala Ala Asp Val Glu Val Val Leu Pro Trp Arg
            30                  35                  40

gtg cgc ccc gac gac gtg cac ctg ccg ccg ctg ccc gca gcc ccc ggg      197
Val Arg Pro Asp Asp Val His Leu Pro Pro Leu Pro Ala Ala Pro Gly
        45                  50                  55

ccc cga cgg cgg cga cgc ccc cgc acg ccc cca gcc gcc ccg cgc gcc      245
Pro Arg Arg Arg Arg Arg Pro Arg Thr Pro Pro Ala Ala Pro Arg Ala
    60                  65                  70

cgg ccc gga gag cgc gcc ctg ctg ctg cac ctg ccg gcc ttc ggg cgc      293
Arg Pro Gly Glu Arg Ala Leu Leu Leu His Leu Pro Ala Phe Gly Arg
75                  80                  85                  90

gac ctg tac ctt cag ctg cgc cgc gac ctg cgc ttc ctg tcc cga ggc      341
Asp Leu Tyr Leu Gln Leu Arg Arg Asp Leu Arg Phe Leu Ser Arg Gly
                95                  100                 105

ttc gag gtg gag gag gcg ggc gcg gcc cgg cgc cgc ggc cgc ccc gcc      389
Phe Glu Val Glu Glu Ala Gly Ala Ala Arg Arg Arg Gly Arg Pro Ala
            110                 115                 120

gag ctg tgc ttc tac tcg ggc cgt gtg ctc ggc cac ccc ggc tcc ctc      437
Glu Leu Cys Phe Tyr Ser Gly Arg Val Leu Gly His Pro Gly Ser Leu
        125                 130                 135

gtc tcg ctc agc gcc tgc ggc gcc gcc ggc ggc ctg gtt ggc ctc att      485
Val Ser Leu Ser Ala Cys Gly Ala Ala Gly Gly Leu Val Gly Leu Ile
    140                 145                 150

cag ctt ggg cag gag cag gtg cta atc cag ccc ctc aac aac tcc cag      533
```

```
Gln Leu Gly Gln Glu Gln Val Leu Ile Gln Pro Leu Asn Asn Ser Gln
155                 160                 165                 170

ggc cca ttc agt gga cga gaa cat ctg atc agg cgc aaa tgg tcc ttg      581
Gly Pro Phe Ser Gly Arg Glu His Leu Ile Arg Arg Lys Trp Ser Leu
                175                 180                 185

acc ccc agc cct tct gct gag gcc cag aga cct gag cag ctc tgc aag      629
Thr Pro Ser Pro Ser Ala Glu Ala Gln Arg Pro Glu Gln Leu Cys Lys
            190                 195                 200

gtt cta aca gaa aag aag aag ccg acg tgg ggc agg cct tcg cgg gac      677
Val Leu Thr Glu Lys Lys Lys Pro Thr Trp Gly Arg Pro Ser Arg Asp
        205                 210                 215

tgg cgg gag cgg agg aac gct atc cgg ctc acc agc gag cac acg gtg      725
Trp Arg Glu Arg Arg Asn Ala Ile Arg Leu Thr Ser Glu His Thr Val
    220                 225                 230

gag acc ctg gtg gtg gcc gac gcc gac atg gtg cag tac cac ggg gcc      773
Glu Thr Leu Val Val Ala Asp Ala Asp Met Val Gln Tyr His Gly Ala
235                 240                 245                 250

gag gcc gcc cag agg ttc atc ctg acc gtc atg aac atg gta tac aat      821
Glu Ala Ala Gln Arg Phe Ile Leu Thr Val Met Asn Met Val Tyr Asn
                255                 260                 265

atg ttt cag cac cag agc ctg ggg att aaa att aac att caa gtg acc      869
Met Phe Gln His Gln Ser Leu Gly Ile Lys Ile Asn Ile Gln Val Thr
            270                 275                 280

aag ctt gtc ctg cta cga caa cgt ccc gct aag ttg tcc att ggg cac      917
Lys Leu Val Leu Leu Arg Gln Arg Pro Ala Lys Leu Ser Ile Gly His
        285                 290                 295

cat ggt gag cgg tcc ctg gag agc ttc tgt cac tgg cag aac gag gag      965
His Gly Glu Arg Ser Leu Glu Ser Phe Cys His Trp Gln Asn Glu Glu
    300                 305                 310

tat gga gga gcg cga tac ctc ggc aat aac cag gtt ccc ggc ggg aag     1013
Tyr Gly Gly Ala Arg Tyr Leu Gly Asn Asn Gln Val Pro Gly Gly Lys
315                 320                 325                 330

gac gac ccg ccc ctg gtg gat gct gct gtg ttt gtg acc agg aca gat     1061
Asp Asp Pro Pro Leu Val Asp Ala Ala Val Phe Val Thr Arg Thr Asp
                335                 340                 345

ttc tgt gta cac aaa gat gaa ccg tgt gac act gtt gga att gct tac     1109
Phe Cys Val His Lys Asp Glu Pro Cys Asp Thr Val Gly Ile Ala Tyr
            350                 355                 360

tta gga ggt gtg tgc agt gct aag agg aag tgt gtg ctt gcc gaa gac     1157
Leu Gly Gly Val Cys Ser Ala Lys Arg Lys Cys Val Leu Ala Glu Asp
        365                 370                 375

aat ggt ctc aat ttg gcc ttt acc atc gcc cat gag ctg ggc cac aac     1205
Asn Gly Leu Asn Leu Ala Phe Thr Ile Ala His Glu Leu Gly His Asn
    380                 385                 390

ttg ggc atg aac cac gac gat gac cac tca tct tgc gct ggc agg tcc     1253
Leu Gly Met Asn His Asp Asp Asp His Ser Ser Cys Ala Gly Arg Ser
395                 400                 405                 410

cac atc atg tca gga gag tgg gtg aaa ggc cgg aac cca agt gac ctc     1301
His Ile Met Ser Gly Glu Trp Val Lys Gly Arg Asn Pro Ser Asp Leu
                415                 420                 425

tct tgg tcc tcc tgc agc cga gat gac ctt gaa aac ttc ctc aag tca     1349
Ser Trp Ser Ser Cys Ser Arg Asp Asp Leu Glu Asn Phe Leu Lys Ser
            430                 435                 440

aaa gtc agc acc tgc ttg cta gtc acg gac ccc aga agc cag cac aca     1397
Lys Val Ser Thr Cys Leu Leu Val Thr Asp Pro Arg Ser Gln His Thr
        445                 450                 455

gta cgc ctc ccg cac aag ctg ccg ggc atg cac tac agt gcc aac gag     1445
Val Arg Leu Pro His Lys Leu Pro Gly Met His Tyr Ser Ala Asn Glu
    460                 465                 470

cag tgc cag atc ctg ttt ggc atg aat gcc acc ttc tgc aga aac atg     1493
```

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Gln Cys Gln Ile Leu Phe Gly Met Asn Ala Thr Phe Cys Arg Asn Met
475                 480                 485                 490

gag cat cta atg tgt gct gga ctg tgg tgc ctg gta gaa gga gac aca      1541
Glu His Leu Met Cys Ala Gly Leu Trp Cys Leu Val Glu Gly Asp Thr
                495                 500                 505

tcc tgc aag acc aag ctg gac cct ccc ctg gat ggc acc gag tgt ggg      1589
Ser Cys Lys Thr Lys Leu Asp Pro Pro Leu Asp Gly Thr Glu Cys Gly
            510                 515                 520

gca gac aag tgg tgc cgc gcg ggg gag tgc gtg agc aag acg ccc atc      1637
Ala Asp Lys Trp Cys Arg Ala Gly Glu Cys Val Ser Lys Thr Pro Ile
        525                 530                 535

ccg gag cat gtg gac gga gac tgg agc ccg tgg ggc gcc tgg agc atg      1685
Pro Glu His Val Asp Gly Asp Trp Ser Pro Trp Gly Ala Trp Ser Met
    540                 545                 550

tgc agc cga aca tgt ggg acg gga gcc cgc ttc agg cag agg aaa tgt      1733
Cys Ser Arg Thr Cys Gly Thr Gly Ala Arg Phe Arg Gln Arg Lys Cys
555                 560                 565                 570

gac aac ccc ccc cct ggg cct gga ggc aca cac tgc ccg ggt gcc agt      1781
Asp Asn Pro Pro Pro Gly Pro Gly Gly Thr His Cys Pro Gly Ala Ser
                575                 580                 585

gta gaa cat gcg gtc tgc gag aac ctg ccc tgc ccc aag ggt ctg ccc      1829
Val Glu His Ala Val Cys Glu Asn Leu Pro Cys Pro Lys Gly Leu Pro
            590                 595                 600

agc ttc cgg gac cag cag tgc cag gca cac gac cgg ctg agc ccc aag      1877
Ser Phe Arg Asp Gln Gln Cys Gln Ala His Asp Arg Leu Ser Pro Lys
        605                 610                 615

aag aaa ggc ctg ctg aca gcc gtg gtg gtt gac gat aag cca tgt gaa      1925
Lys Lys Gly Leu Leu Thr Ala Val Val Val Asp Asp Lys Pro Cys Glu
    620                 625                 630

ctc tac tgc tcg ccc ctc ggg aag gag tcc cca ctg ctg gtg gcc gac      1973
Leu Tyr Cys Ser Pro Leu Gly Lys Glu Ser Pro Leu Leu Val Ala Asp
635                 640                 645                 650

agg gtc ctg gac ggt aca ccc tgc ggg ccc tac gag act gat ctc tgc      2021
Arg Val Leu Asp Gly Thr Pro Cys Gly Pro Tyr Glu Thr Asp Leu Cys
                655                 660                 665

gtg cac ggc aag tgc cag aaa atc ggc tgt gac ggc atc atc ggg tct      2069
Val His Gly Lys Cys Gln Lys Ile Gly Cys Asp Gly Ile Ile Gly Ser
            670                 675                 680

gca gcc aaa gag gac aga tgc ggg gtc tgc agc ggg gac ggc aag acc      2117
Ala Ala Lys Glu Asp Arg Cys Gly Val Cys Ser Gly Asp Gly Lys Thr
        685                 690                 695

tgc cac ttg gtg aag ggc gac ttc agc cac gcc cgg ggg aca gct ctc      2165
Cys His Leu Val Lys Gly Asp Phe Ser His Ala Arg Gly Thr Ala Leu
    700                 705                 710

aaa gac tcg ggt aag ggg tcc atc aac agt gac tgg aag ata gag ctc      2213
Lys Asp Ser Gly Lys Gly Ser Ile Asn Ser Asp Trp Lys Ile Glu Leu
715                 720                 725                 730

ccc gga gag ttc cag att gca ggc aca act gtt cgc tat gtg aga agg      2261
Pro Gly Glu Phe Gln Ile Ala Gly Thr Thr Val Arg Tyr Val Arg Arg
                735                 740                 745

ggg ctg tgg gag aag atc tct gcc aag gga cca acc aaa cta ccg ctg      2309
Gly Leu Trp Glu Lys Ile Ser Ala Lys Gly Pro Thr Lys Leu Pro Leu
            750                 755                 760

cac ttg atg gtg ttg tta ttt cac gac caa gat tat gga att cat tat      2357
His Leu Met Val Leu Leu Phe His Asp Gln Asp Tyr Gly Ile His Tyr
        765                 770                 775

gaa tac act gtt cct gta aac cgc act gcg gaa aat caa agc gaa cca      2405
Glu Tyr Thr Val Pro Val Asn Arg Thr Ala Glu Asn Gln Ser Glu Pro
    780                 785                 790

gaa aaa ccg cag gac tct ttg ttc atc tgg acc cac agc ggc tgg gaa      2453
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Glu Lys Pro Gln Asp Ser Leu Phe Ile Trp Thr His Ser Gly Trp Glu
795                 800                 805                 810

ggg tgc agt gtg cag tgc ggc gga ggg gag cgc aga acc atc gtc tcg      2501
Gly Cys Ser Val Gln Cys Gly Gly Gly Glu Arg Arg Thr Ile Val Ser
                815                 820                 825

tgt aca cgg att gtc aac aag acc aca act ctg gtg aac gac agt gac      2549
Cys Thr Arg Ile Val Asn Lys Thr Thr Thr Leu Val Asn Asp Ser Asp
            830                 835                 840

tgc cct caa gca agc cgc cca gag ccc cag gtc cga agg tgc aac ttg      2597
Cys Pro Gln Ala Ser Arg Pro Glu Pro Gln Val Arg Arg Cys Asn Leu
        845                 850                 855

cac ccc tgc cag tca cgg tgg gtg gca ggc ccg tgg agc ccc tgc tcg      2645
His Pro Cys Gln Ser Arg Trp Val Ala Gly Pro Trp Ser Pro Cys Ser
    860                 865                 870

gcg acc tgt gag aaa ggc ttc cag cac cgg gag gtg acc tgc gtg tac      2693
Ala Thr Cys Glu Lys Gly Phe Gln His Arg Glu Val Thr Cys Val Tyr
875                 880                 885                 890

cag ctg cag aac ggc aca cac gtc gct acg cgg ccc ctc tac tgc ccg      2741
Gln Leu Gln Asn Gly Thr His Val Ala Thr Arg Pro Leu Tyr Cys Pro
                895                 900                 905

ggc ccc cgg ccg gcg gca gtg cag agc tgt gaa ggc cag gac tgc ctg      2789
Gly Pro Arg Pro Ala Ala Val Gln Ser Cys Glu Gly Gln Asp Cys Leu
            910                 915                 920

tcc atc tgg gag gcg tct gag tgg tca cag tgc tct gcc agc tgt ggt      2837
Ser Ile Trp Glu Ala Ser Glu Trp Ser Gln Cys Ser Ala Ser Cys Gly
        925                 930                 935

aaa ggg gtg tgg aaa cgg acc gtg gcg tgc acc aac tca caa ggg aaa      2885
Lys Gly Val Trp Lys Arg Thr Val Ala Cys Thr Asn Ser Gln Gly Lys
    940                 945                 950

tgc gac gca tcc acg agg ccg aga gcc gag gag gcc tgc gag gac tac      2933
Cys Asp Ala Ser Thr Arg Pro Arg Ala Glu Glu Ala Cys Glu Asp Tyr
955                 960                 965                 970

tca ggc tgc tac gag tgg aaa act ggg gac tgg tct acg tgc tcg tcg      2981
Ser Gly Cys Tyr Glu Trp Lys Thr Gly Asp Trp Ser Thr Cys Ser Ser
                975                 980                 985

acc tgc ggg aag ggc ctg cag tcc cgg gtg gtg cag tgc atg  cac aag      3029
Thr Cys Gly Lys Gly Leu Gln Ser Arg Val Val Gln Cys Met  His Lys
            990                 995                1000

gtc aca ggg  cgc cac ggc agc gag  tgc ccc gcc ctc tcg  aag cct      3074
Val Thr Gly  Arg His Gly Ser Glu  Cys Pro Ala Leu Ser  Lys Pro
        1005                1010                1015

gcc ccc tac  aga cag tgc tac cag  gag gtc tgc aac gac  agg atc      3119
Ala Pro Tyr  Arg Gln Cys Tyr Gln  Glu Val Cys Asn Asp  Arg Ile
    1020                1025                1030

aac gcc aac  acc atc acc tcc ccc  cgc ctt gct gct ctg  acc tac      3164
Asn Ala Asn  Thr Ile Thr Ser Pro  Arg Leu Ala Ala Leu  Thr Tyr
    1035                1040                1045

aaa tgc aca  cga gac cag tgg acg  gta tat tgc cgg gtc  atc cga      3209
Lys Cys Thr  Arg Asp Gln Trp Thr  Val Tyr Cys Arg Val  Ile Arg
    1050                1055                1060

gaa aag aac  ctc tgc cag gac atg  cgg tgg tac cag cgc  tgc tgc      3254
Glu Lys Asn  Leu Cys Gln Asp Met  Arg Trp Tyr Gln Arg  Cys Cys
    1065                1070                1075

cag acc tgc  agg gac ttc tat gca  aac aag atg cgc cag  cca ccg      3299
Gln Thr Cys  Arg Asp Phe Tyr Ala  Asn Lys Met Arg Gln  Pro Pro
    1080                1085                1090

ccg agc tcg  tga cacgcagtcc caagggtcgc tcaaagctca gactcaggtc        3351
Pro Ser Ser
    1095

tgaaacccac ccacccgcaa gcctaccagc cttgtggcca cgcccccacc cggctgccac   3411
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aagaatccaa ctgcatagaa catgagcgtg gacttggaaa aaaaaaaaaa aaaaaaaaa 3470

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<400> 6

Met Cys Asp Gly Ala Leu Leu Pro Pro Leu Val Leu Pro Val Leu Leu
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Leu Leu Val Trp Gly Leu Asp Pro Gly Thr Ala Val Gly Asp Ala Ala
20 25 30

Ala Asp Val Glu Val Val Leu Pro Trp Arg Val Arg Pro Asp Asp Val
35 40 45

His Leu Pro Pro Leu Pro Ala Ala Pro Gly Pro Arg Arg Arg Arg Arg
50 55 60

Pro Arg Thr Pro Pro Ala Ala Pro Arg Ala Arg Pro Gly Glu Arg Ala
65 70 75 80

Leu Leu Leu His Leu Pro Ala Phe Gly Arg Asp Leu Tyr Leu Gln Leu
85 90 95

Arg Arg Asp Leu Arg Phe Leu Ser Arg Gly Phe Glu Val Glu Glu Ala
100 105 110

Gly Ala Ala Arg Arg Arg Gly Arg Pro Ala Glu Leu Cys Phe Tyr Ser
115 120 125

Gly Arg Val Leu Gly His Pro Gly Ser Leu Val Ser Leu Ser Ala Cys
130 135 140

Gly Ala Ala Gly Gly Leu Val Gly Leu Ile Gln Leu Gly Gln Glu Gln
145 150 155 160

Val Leu Ile Gln Pro Leu Asn Asn Ser Gln Gly Pro Phe Ser Gly Arg
165 170 175

Glu His Leu Ile Arg Arg Lys Trp Ser Leu Thr Pro Ser Pro Ser Ala
180 185 190

Glu Ala Gln Arg Pro Glu Gln Leu Cys Lys Val Leu Thr Glu Lys Lys
195 200 205

Lys Pro Thr Trp Gly Arg Pro Ser Arg Asp Trp Arg Glu Arg Arg Asn
210 215 220

Ala Ile Arg Leu Thr Ser Glu His Thr Val Glu Thr Leu Val Val Ala
225 230 235 240

Asp Ala Asp Met Val Gln Tyr His Gly Ala Glu Ala Ala Gln Arg Phe
245 250 255

Ile Leu Thr Val Met Asn Met Val Tyr Asn Met Phe Gln His Gln Ser
260 265 270

Leu Gly Ile Lys Ile Asn Ile Gln Val Thr Lys Leu Val Leu Leu Arg
275 280 285

Gln Arg Pro Ala Lys Leu Ser Ile Gly His His Gly Glu Arg Ser Leu
290 295 300

Glu Ser Phe Cys His Trp Gln Asn Glu Glu Tyr Gly Gly Ala Arg Tyr
305 310 315 320

Leu Gly Asn Asn Gln Val Pro Gly Gly Lys Asp Asp Pro Pro Leu Val
325 330 335

Asp Ala Ala Val Phe Val Thr Arg Thr Asp Phe Cys Val His Lys Asp
340 345 350

Glu Pro Cys Asp Thr Val Gly Ile Ala Tyr Leu Gly Gly Val Cys Ser
355 360 365

Ala Lys Arg Lys Cys Val Leu Ala Glu Asp Asn Gly Leu Asn Leu Ala
370 375 380

Phe Thr Ile Ala His Glu Leu Gly His Asn Leu Gly Met Asn His Asp
385 390 395 400

Asp Asp His Ser Ser Cys Ala Gly Arg Ser His Ile Met Ser Gly Glu
405 410 415

Trp Val Lys Gly Arg Asn Pro Ser Asp Leu Ser Trp Ser Ser Cys Ser
420 425 430

Arg Asp Asp Leu Glu Asn Phe Leu Lys Ser Lys Val Ser Thr Cys Leu
435 440 445

Leu Val Thr Asp Pro Arg Ser Gln His Thr Val Arg Leu Pro His Lys
450 455 460

Leu Pro Gly Met His Tyr Ser Ala Asn Glu Gln Cys Gln Ile Leu Phe
465 470 475 480

Gly Met Asn Ala Thr Phe Cys Arg Asn Met Glu His Leu Met Cys Ala
485 490 495

Gly Leu Trp Cys Leu Val Glu Gly Asp Thr Ser Cys Lys Thr Lys Leu
500 505 510

Asp Pro Pro Leu Asp Gly Thr Glu Cys Gly Ala Asp Lys Trp Cys Arg
515 520 525

Ala Gly Glu Cys Val Ser Lys Thr Pro Ile Pro Glu His Val Asp Gly
530 535 540

Asp Trp Ser Pro Trp Gly Ala Trp Ser Met Cys Ser Arg Thr Cys Gly
545 550 555 560

Thr Gly Ala Arg Phe Arg Gln Arg Lys Cys Asp Asn Pro Pro Pro Gly
565 570 575

Pro Gly Gly Thr His Cys Pro Gly Ala Ser Val Glu His Ala Val Cys
580 585 590

Glu Asn Leu Pro Cys Pro Lys Gly Leu Pro Ser Phe Arg Asp Gln Gln
595 600 605

Cys Gln Ala His Asp Arg Leu Ser Pro Lys Lys Lys Gly Leu Leu Thr
610 615 620

Ala Val Val Val Asp Asp Lys Pro Cys Glu Leu Tyr Cys Ser Pro Leu
625 630 635 640

Gly Lys Glu Ser Pro Leu Leu Val Ala Asp Arg Val Leu Asp Gly Thr
645 650 655

Pro Cys Gly Pro Tyr Glu Thr Asp Leu Cys Val His Gly Lys Cys Gln
660 665 670

Lys Ile Gly Cys Asp Gly Ile Ile Gly Ser Ala Ala Lys Glu Asp Arg
675 680 685

Cys Gly Val Cys Ser Gly Asp Gly Lys Thr Cys His Leu Val Lys Gly
690 695 700

Asp Phe Ser His Ala Arg Gly Thr Ala Leu Lys Asp Ser Gly Lys Gly
705 710 715 720

Ser Ile Asn Ser Asp Trp Lys Ile Glu Leu Pro Gly Glu Phe Gln Ile
725 730 735

Ala Gly Thr Thr Val Arg Tyr Val Arg Arg Gly Leu Trp Glu Lys Ile
740 745 750

Ser Ala Lys Gly Pro Thr Lys Leu Pro Leu His Leu Met Val Leu Leu
755 760 765

Phe His Asp Gln Asp Tyr Gly Ile His Tyr Glu Tyr Thr Val Pro Val
770 775 780

Asn Arg Thr Ala Glu Asn Gln Ser Glu Pro Glu Lys Pro Gln Asp Ser
785 790 795 800

Leu Phe Ile Trp Thr His Ser Gly Trp Glu Gly Cys Ser Val Gln Cys
805 810 815

Gly Gly Gly Glu Arg Arg Thr Ile Val Ser Cys Thr Arg Ile Val Asn
820 825 830

Lys Thr Thr Thr Leu Val Asn Asp Ser Asp Cys Pro Gln Ala Ser Arg
835 840 845

Pro Glu Pro Gln Val Arg Arg Cys Asn Leu His Pro Cys Gln Ser Arg
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Trp Val Ala Gly Pro Trp Ser Pro Cys Ser Ala Thr Cys Glu Lys Gly
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Phe Gln His Arg Glu Val Thr Cys Val Tyr Gln Leu Gln Asn Gly Thr
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His Val Ala Thr Arg Pro Leu Tyr Cys Pro Gly Pro Arg Pro Ala Ala
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Val Gln Ser Cys Glu Gly Gln Asp Cys Leu Ser Ile Trp Glu Ala Ser
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Glu Trp Ser Gln Cys Ser Ala Ser Cys Gly Lys Gly Val Trp Lys Arg
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Thr Val Ala Cys Thr Asn Ser Gln Gly Lys Cys Asp Ala Ser Thr Arg
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Pro Arg Ala Glu Glu Ala Cys Glu Asp Tyr Ser Gly Cys Tyr Glu Trp
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Lys Thr Gly Asp Trp Ser Thr Cys Ser Ser Thr Cys Gly Lys Gly Leu
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Gln Ser Arg Val Val Gln Cys Met His Lys Val Thr Gly Arg His Gly
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Ser Glu Cys Pro Ala Leu Ser Lys Pro Ala Pro Tyr Arg Gln Cys
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Tyr Gln Glu Val Cys Asn Asp Arg Ile Asn Ala Asn Thr Ile Thr
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Ser Pro Arg Leu Ala Ala Leu Thr Tyr Lys Cys Thr Arg Asp Gln
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Trp Thr Val Tyr Cys Arg Val Ile Arg Glu Lys Asn Leu Cys Gln
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Pro Glu Tyr Ser Ala Glu Tyr Ser Ala Glu Tyr Ser Val Ser Leu Pro
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Ser Asp Pro Asp Arg Gly Val Gly Arg Thr His Glu Ile Ser Val Arg
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Asn Ser Gly Ser Cys Leu Cys Leu Pro Arg Phe Met Arg Leu Thr Phe
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Val Pro Glu Ser Leu Glu Asn Leu Tyr Gln Thr Tyr Phe Lys Arg Gln
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cgc cac gag acc ctg ctg gtg ctg gtg gtc ttt gca gcc ctc ttt gac 414

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Arg His Glu Thr Leu Leu Val Leu Val Val Phe Ala Ala Leu Phe Asp
 75                  80                  85

tgc tac gtg gtg gtc atg tgt gct gtg gtc ttc tcc agc gac aag ctg      462
Cys Tyr Val Val Val Met Cys Ala Val Val Phe Ser Ser Asp Lys Leu
90                  95                 100                 105

gct ccc ctc gcc gtg gct gga att gga ctg gtg ttg gac atc atc ctc      510
Ala Pro Leu Ala Val Ala Gly Ile Gly Leu Val Leu Asp Ile Ile Leu
                110                 115                 120

ttc gtg ctc tgc aaa aag ggg ctg ctc ccg gac cgg gtc acc cgc aga      558
Phe Val Leu Cys Lys Lys Gly Leu Leu Pro Asp Arg Val Thr Arg Arg
            125                 130                 135

gtg ctg ccc tac gtg ctg tgg ctg ctc ata acc gcc cag atc ttc tcc      606
Val Leu Pro Tyr Val Leu Trp Leu Leu Ile Thr Ala Gln Ile Phe Ser
        140                 145                 150

tac ctg ggc ctg aac ttc gcg cgt gcc cac gcg gct agt gac acg gtg      654
Tyr Leu Gly Leu Asn Phe Ala Arg Ala His Ala Ala Ser Asp Thr Val
    155                 160                 165

ggc tgg cag gtc ttc ttt gtc ttc tcc ttc ttc atc acg ctg ccc ctc      702
Gly Trp Gln Val Phe Phe Val Phe Ser Phe Phe Ile Thr Leu Pro Leu
170                 175                 180                 185

agc ctc agc ccc atc gtg atc atc tcc gtg gtc tcc tgt gtg gtg cac      750
Ser Leu Ser Pro Ile Val Ile Ile Ser Val Val Ser Cys Val Val His
                190                 195                 200

acg ttg gtc ctg ggg gtc acc gtg gcc cag cag cag cag gag gag ctc      798
Thr Leu Val Leu Gly Val Thr Val Ala Gln Gln Gln Gln Glu Glu Leu
            205                 210                 215

aag ggg atg cag ctg ctg cgg gag atc ctg gcc aac gtc ttc ctc tac      846
Lys Gly Met Gln Leu Leu Arg Glu Ile Leu Ala Asn Val Phe Leu Tyr
        220                 225                 230

ctg tgc gcc atc gct gtg ggc atc atg tcc tac tac atg gct gac cgc      894
Leu Cys Ala Ile Ala Val Gly Ile Met Ser Tyr Tyr Met Ala Asp Arg
    235                 240                 245

aag cac cgc aag gcc ttc ctg gag gcc cgc cag tcg ctg gag gtg aag      942
Lys His Arg Lys Ala Phe Leu Glu Ala Arg Gln Ser Leu Glu Val Lys
250                 255                 260                 265

atg aac ctg gaa gag cag agc cag cag cag gag aac ctc atg ctt tcc      990
Met Asn Leu Glu Glu Gln Ser Gln Gln Gln Glu Asn Leu Met Leu Ser
                270                 275                 280

atc ctg ccc aag cac gtg gct gac gag atg ctg aaa gac atg aag aaa     1038
Ile Leu Pro Lys His Val Ala Asp Glu Met Leu Lys Asp Met Lys Lys
            285                 290                 295

gac gag agc cag aag gac cag cag cag ttc aac acc atg tac atg tac     1086
Asp Glu Ser Gln Lys Asp Gln Gln Gln Phe Asn Thr Met Tyr Met Tyr
        300                 305                 310

cgt cac gag aac gtc agc atc ctc ttt gcc gac atc gtg ggc ttt acc     1134
Arg His Glu Asn Val Ser Ile Leu Phe Ala Asp Ile Val Gly Phe Thr
    315                 320                 325

cag ctg tct tct gcc tgc agt gcc cag gag ctt gtg aag ctg ctc aac     1182
Gln Leu Ser Ser Ala Cys Ser Ala Gln Glu Leu Val Lys Leu Leu Asn
330                 335                 340                 345

gag ctc ttt gcc cgc ttt gac aag ctg gca gct aaa tac cac cag ctg     1230
Glu Leu Phe Ala Arg Phe Asp Lys Leu Ala Ala Lys Tyr His Gln Leu
                350                 355                 360

cgg att aag atc ctg ggc gac tgc tac tac tgc atc tgc ggc ttg cct     1278
Arg Ile Lys Ile Leu Gly Asp Cys Tyr Tyr Cys Ile Cys Gly Leu Pro
            365                 370                 375

gac tac cgg gag gac cac gcc gtc tgc tcc atc ctc atg ggg ctg gcc     1326
Asp Tyr Arg Glu Asp His Ala Val Cys Ser Ile Leu Met Gly Leu Ala
        380                 385                 390

atg gtg gag gcc atc tcg tat gtg cgg gag aag acc aag act ggg gtg     1374
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Met Val Glu Ala Ile Ser Tyr Val Arg Glu Lys Thr Lys Thr Gly Val
395                 400                 405

gac atg cgt gtg ggg gtg cac acg ggc acc gtg ctg ggg ggc gtc ctg      1422
Asp Met Arg Val Gly Val His Thr Gly Thr Val Leu Gly Gly Val Leu
410                 415                 420                 425

ggc cag aag cgc tgg cag tac gac gtg tgg tcg act gat gtc act gta      1470
Gly Gln Lys Arg Trp Gln Tyr Asp Val Trp Ser Thr Asp Val Thr Val
                430                 435                 440

gcc aac aag atg gag gcc ggc ggc atc cct ggg cgc gtg cac atc tcc      1518
Ala Asn Lys Met Glu Ala Gly Gly Ile Pro Gly Arg Val His Ile Ser
            445                 450                 455

cag agc acc atg gac tgc ctg aaa ggg gag ttt gat gtg gag cca ggc      1566
Gln Ser Thr Met Asp Cys Leu Lys Gly Glu Phe Asp Val Glu Pro Gly
        460                 465                 470

gat ggg ggc agc cgc tgt gat tac cta gaa gag aag ggt att gaa acc      1614
Asp Gly Gly Ser Arg Cys Asp Tyr Leu Glu Glu Lys Gly Ile Glu Thr
    475                 480                 485

tac ctc atc att gcc tcc aag cca gag gtg aag aaa aca gcc acc cag      1662
Tyr Leu Ile Ile Ala Ser Lys Pro Glu Val Lys Lys Thr Ala Thr Gln
490                 495                 500                 505

aat ggc ctc aat ggc tcg gcc ctg ccc aat gga gca cca gct tcc tca      1710
Asn Gly Leu Asn Gly Ser Ala Leu Pro Asn Gly Ala Pro Ala Ser Ser
                510                 515                 520

aag tcc agc tcc cct gcc ctc att gag acc aag gag ccc aac ggg agt      1758
Lys Ser Ser Ser Pro Ala Leu Ile Glu Thr Lys Glu Pro Asn Gly Ser
            525                 530                 535

gcc cac agc agt ggg tcc acg tcg gag aag ccc gag gag cag gat gcc      1806
Ala His Ser Ser Gly Ser Thr Ser Glu Lys Pro Glu Glu Gln Asp Ala
        540                 545                 550

cag gcc gac aac ccc tca ttc ccc aac cca cgc cgg agg ctg cgc ctg      1854
Gln Ala Asp Asn Pro Ser Phe Pro Asn Pro Arg Arg Arg Leu Arg Leu
    555                 560                 565

cag gac ctg gct gac cga gtg gtg gat gcc tct gaa gat gag cac gag      1902
Gln Asp Leu Ala Asp Arg Val Val Asp Ala Ser Glu Asp Glu His Glu
570                 575                 580                 585

ctc aac cag ctg ctc aac gag gcc ctg ctt gag cga gag tcc gcc caa      1950
Leu Asn Gln Leu Leu Asn Glu Ala Leu Leu Glu Arg Glu Ser Ala Gln
                590                 595                 600

gta gta aag aag aga aac acc ttc ctc ttg tcc atg cgg ttc atg gac      1998
Val Val Lys Lys Arg Asn Thr Phe Leu Leu Ser Met Arg Phe Met Asp
            605                 610                 615

ccc gag atg gaa acc cgc tac tcg gtg gag aag gag aag cag agt ggg      2046
Pro Glu Met Glu Thr Arg Tyr Ser Val Glu Lys Glu Lys Gln Ser Gly
        620                 625                 630

gct gcc ttc agc tgc tcc tgc gtc gtc ctg ctc tgc acg gcc ctg gtc      2094
Ala Ala Phe Ser Cys Ser Cys Val Val Leu Leu Cys Thr Ala Leu Val
    635                 640                 645

gag ata ctc atc gac ccc tgg cta atg aca aac tat gtg acc ttc atg      2142
Glu Ile Leu Ile Asp Pro Trp Leu Met Thr Asn Tyr Val Thr Phe Met
650                 655                 660                 665

gtg ggg gag att ctg ctc ctc atc ctg acc atc tgc tcc ctg gct gcc      2190
Val Gly Glu Ile Leu Leu Leu Ile Leu Thr Ile Cys Ser Leu Ala Ala
                670                 675                 680

atc ttt ccc cgg gcc ttt cct aag aag ctt gtg gcc ttc tca act tgg      2238
Ile Phe Pro Arg Ala Phe Pro Lys Lys Leu Val Ala Phe Ser Thr Trp
            685                 690                 695

att gac cgg acc cgc tgg gcc agg aac acc tgg gcc atg ctc gcc atc      2286
Ile Asp Arg Thr Arg Trp Ala Arg Asn Thr Trp Ala Met Leu Ala Ile
        700                 705                 710

ttc atc ctg gtg atg gca aat gtc gtg gac atg ctc agc tgt ctc cag      2334
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Phe Ile Leu Val Met Ala Asn Val Val Asp Met Leu Ser Cys Leu Gln
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tac tac acg gga ccc agc aat gca acg gca ggg atg gag acg gag ggc      2382
Tyr Tyr Thr Gly Pro Ser Asn Ala Thr Ala Gly Met Glu Thr Glu Gly
730                 735                 740                 745

agc tgc ctg gag aac ccc aag tat tac aac tat gtg gcc gtg ctg tcc      2430
Ser Cys Leu Glu Asn Pro Lys Tyr Tyr Asn Tyr Val Ala Val Leu Ser
                750                 755                 760

ctc atc gcc acc atc atg ctg gtg cag gtc agc cac atg gtg aag ctc      2478
Leu Ile Ala Thr Ile Met Leu Val Gln Val Ser His Met Val Lys Leu
            765                 770                 775

acg ctc atg ctg ctc gtc gca ggc gcc gtg gcc acc atc aac ctc tat      2526
Thr Leu Met Leu Leu Val Ala Gly Ala Val Ala Thr Ile Asn Leu Tyr
        780                 785                 790

gcc tgg cgt ccc gtc ttt gat gaa tac gac cac aag cgt ttt cgg gag      2574
Ala Trp Arg Pro Val Phe Asp Glu Tyr Asp His Lys Arg Phe Arg Glu
    795                 800                 805

cac gac tta cct atg gtg gcc tta gag cag atg caa gga ttc aac cct      2622
His Asp Leu Pro Met Val Ala Leu Glu Gln Met Gln Gly Phe Asn Pro
810                 815                 820                 825

ggg ctc aat ggc act gac agg ctg ccc ctg gtg cct tcc aag tac tct      2670
Gly Leu Asn Gly Thr Asp Arg Leu Pro Leu Val Pro Ser Lys Tyr Ser
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atg acg gtg atg gtg ttc ctc atg atg ctc agc ttc tac tac ttc tcc      2718
Met Thr Val Met Val Phe Leu Met Met Leu Ser Phe Tyr Tyr Phe Ser
            845                 850                 855

cgc cac gta gaa aaa ctg gca cgg aca ctt ttc ttg tgg aag att gag      2766
Arg His Val Glu Lys Leu Ala Arg Thr Leu Phe Leu Trp Lys Ile Glu
        860                 865                 870

gtc cac gac cag aag gaa cgt gtc tat gag atg cga cgc tgg aac gag      2814
Val His Asp Gln Lys Glu Arg Val Tyr Glu Met Arg Arg Trp Asn Glu
    875                 880                 885

gcc ttg gtc acc aac atg ttg cct gag cac gtg gca cgc cat ttc ctg      2862
Ala Leu Val Thr Asn Met Leu Pro Glu His Val Ala Arg His Phe Leu
890                 895                 900                 905

ggg tcc aag aag aga gat gag gag ctg tat agc cag acg tat gat gag      2910
Gly Ser Lys Lys Arg Asp Glu Glu Leu Tyr Ser Gln Thr Tyr Asp Glu
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att gga gtc atg ttt gcc tcc ctg ccc aac ttt gct gac ttc tac aca      2958
Ile Gly Val Met Phe Ala Ser Leu Pro Asn Phe Ala Asp Phe Tyr Thr
            925                 930                 935

gag gag agc atc aac aat ggt ggt att gag tgt ctg cgt ttc ctc aat      3006
Glu Glu Ser Ile Asn Asn Gly Gly Ile Glu Cys Leu Arg Phe Leu Asn
        940                 945                 950

gaa atc atc tca gat ttt gac tct ctc ctg gac aat ccc aag ttc cgg      3054
Glu Ile Ile Ser Asp Phe Asp Ser Leu Leu Asp Asn Pro Lys Phe Arg
    955                 960                 965

gtg atc acc aag atc aaa acc att ggc agc acg tat atg gcg gct tca      3102
Val Ile Thr Lys Ile Lys Thr Ile Gly Ser Thr Tyr Met Ala Ala Ser
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gga gtc acc ccc gat gtc aac acc aat ggc ttt gcc agc tcc aac  aag      3150
Gly Val Thr Pro Asp Val Asn Thr Asn Gly Phe Ala Ser Ser Asn  Lys
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gaa gac aag tcc  gag aga gag cgc tgg  cag cac ctg gct gac  ctg        3195
Glu Asp Lys Ser  Glu Arg Glu Arg Trp  Gln His Leu Ala Asp  Leu
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gcc gac ttc gcg  ctg gcc atg aag gat  acg ctc acc aac atc  aac        3240
Ala Asp Phe Ala  Leu Ala Met Lys Asp  Thr Leu Thr Asn Ile  Asn
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aac cag tcc ttc  aat aac ttc atg ctg  cgc ata ggc atg aac  aaa        3285
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Asp Ile Trp Gly Asn Thr Val Asn Val Ala Ser Arg Met Glu Ser
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acg ggg gtc atg ggc aac att cag gtg gta gaa gaa acc caa gtc 3420
Thr Gly Val Met Gly Asn Ile Gln Val Val Glu Glu Thr Gln Val
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atc ctc cga gag tac ggc ttc cgc ttt gtg agg cga ggc ccc atc 3465
Ile Leu Arg Glu Tyr Gly Phe Arg Phe Val Arg Arg Gly Pro Ile
1095 1100 1105

ttt gtg aag ggg aag ggg gag ctg ctg acc ttc ttc ttg aag ggg 3510
Phe Val Lys Gly Lys Gly Glu Leu Leu Thr Phe Phe Leu Lys Gly
1110 1115 1120

cgg gat aag cta gcc acc ttc ccc aat ggc ccc tct gtc aca ctg 3555
Arg Asp Lys Leu Ala Thr Phe Pro Asn Gly Pro Ser Val Thr Leu
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Pro His Gln Val Val Asp Asn Ser
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Ala Val Val Phe Ser Ser Asp Lys Leu Ala Pro Leu Ala Val Ala Gly
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Ile Gly Leu Val Leu Asp Ile Ile Leu Phe Val Leu Cys Lys Lys Gly
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145 150 155 160

Arg Ala His Ala Ala Ser Asp Thr Val Gly Trp Gln Val Phe Phe Val
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Phe Ser Phe Phe Ile Thr Leu Pro Leu Ser Leu Ser Pro Ile Val Ile
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Ile Ser Val Val Ser Cys Val Val His Thr Leu Val Leu Gly Val Thr
195 200 205

Val Ala Gln Gln Gln Gln Glu Glu Leu Lys Gly Met Gln Leu Leu Arg
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Glu Ile Leu Ala Asn Val Phe Leu Tyr Leu Cys Ala Ile Ala Val Gly
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Ile Met Ser Tyr Tyr Met Ala Asp Arg Lys His Arg Lys Ala Phe Leu
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Glu Ala Arg Gln Ser Leu Glu Val Lys Met Asn Leu Glu Glu Gln Ser
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Asp Glu Met Leu Lys Asp Met Lys Lys Asp Glu Ser Gln Lys Asp Gln
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Gln Gln Phe Asn Thr Met Tyr Met Tyr Arg His Glu Asn Val Ser Ile
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Leu Phe Ala Asp Ile Val Gly Phe Thr Gln Leu Ser Ser Ala Cys Ser
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Ala Gln Glu Leu Val Lys Leu Leu Asn Glu Leu Phe Ala Arg Phe Asp
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Lys Leu Ala Ala Lys Tyr His Gln Leu Arg Ile Lys Ile Leu Gly Asp
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Cys Tyr Tyr Cys Ile Cys Gly Leu Pro Asp Tyr Arg Glu Asp His Ala
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Val Cys Ser Ile Leu Met Gly Leu Ala Met Val Glu Ala Ile Ser Tyr
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Val Arg Glu Lys Thr Lys Thr Gly Val Asp Met Arg Val Gly Val His
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Thr Gly Thr Val Leu Gly Gly Val Leu Gly Gln Lys Arg Trp Gln Tyr
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Asp Val Trp Ser Thr Asp Val Thr Val Ala Asn Lys Met Glu Ala Gly
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Gly Ile Pro Gly Arg Val His Ile Ser Gln Ser Thr Met Asp Cys Leu
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Lys Gly Glu Phe Asp Val Glu Pro Gly Asp Gly Gly Ser Arg Cys Asp
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Tyr Leu Glu Glu Lys Gly Ile Glu Thr Tyr Leu Ile Ile Ala Ser Lys
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Pro Glu Val Lys Lys Thr Ala Thr Gln Asn Gly Leu Asn Gly Ser Ala
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Leu Pro Asn Gly Ala Pro Ala Ser Ser Lys Ser Ser Ser Pro Ala Leu
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Ile Glu Thr Lys Glu Pro Asn Gly Ser Ala His Ser Ser Gly Ser Thr
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Ser Glu Lys Pro Glu Glu Gln Asp Ala Gln Ala Asp Asn Pro Ser Phe
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Pro Asn Pro Arg Arg Arg Leu Arg Leu Gln Asp Leu Ala Asp Arg Val
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Val Asp Ala Ser Glu Asp Glu His Glu Leu Asn Gln Leu Leu Asn Glu
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Ala Leu Leu Glu Arg Glu Ser Ala Gln Val Val Lys Lys Arg Asn Thr
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Phe Leu Leu Ser Met Arg Phe Met Asp Pro Glu Met Glu Thr Arg Tyr
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Ser Val Glu Lys Glu Lys Gln Ser Gly Ala Ala Phe Ser Cys Ser Cys
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Leu Met Thr Asn Tyr Val Thr Phe Met Val Gly Glu Ile Leu Leu Leu
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Lys Lys Leu Val Ala Phe Ser Thr Trp Ile Asp Arg Thr Arg Trp Ala
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Arg Asn Thr Trp Ala Met Leu Ala Ile Phe Ile Leu Val Met Ala Asn
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Val Val Asp Met Leu Ser Cys Leu Gln Tyr Tyr Thr Gly Pro Ser Asn
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Ala Thr Ala Gly Met Glu Thr Glu Gly Ser Cys Leu Glu Asn Pro Lys
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Tyr Tyr Asn Tyr Val Ala Val Leu Ser Leu Ile Ala Thr Ile Met Leu
755 760 765

Val Gln Val Ser His Met Val Lys Leu Thr Leu Met Leu Leu Val Ala
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Glu Tyr Asp His Lys Arg Phe Arg Glu His Asp Leu Pro Met Val Ala
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Met Met Leu Ser Phe Tyr Tyr Phe Ser Arg His Val Glu Lys Leu Ala
850 855 860

Arg Thr Leu Phe Leu Trp Lys Ile Glu Val His Asp Gln Lys Glu Arg
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Val Tyr Glu Met Arg Arg Trp Asn Glu Ala Leu Val Thr Asn Met Leu
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Pro Glu His Val Ala Arg His Phe Leu Gly Ser Lys Lys Arg Asp Glu
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Glu Leu Tyr Ser Gln Thr Tyr Asp Glu Ile Gly Val Met Phe Ala Ser
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Leu Pro Asn Phe Ala Asp Phe Tyr Thr Glu Glu Ser Ile Asn Asn Gly
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Gly Ile Glu Cys Leu Arg Phe Leu Asn Glu Ile Ile Ser Asp Phe Asp
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Ser Leu Leu Asp Asn Pro Lys Phe Arg Val Ile Thr Lys Ile Lys Thr
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Ile Gly Ser Thr Tyr Met Ala Ala Ser Gly Val Thr Pro Asp Val Asn
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Thr Asn Gly Phe Ala Ser Ser Asn Lys Glu Asp Lys Ser Glu Arg Glu
995 1000 1005

Arg Trp Gln His Leu Ala Asp Leu Ala Asp Phe Ala Leu Ala Met
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Lys Asp Thr Leu Thr Asn Ile Asn Asn Gln Ser Phe Asn Asn Phe
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Met Leu Arg Ile Gly Met Asn Lys Gly Gly Val Leu Ala Gly Val
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Ile Gly Ala Arg Lys Pro His Tyr Asp Ile Trp Gly Asn Thr Val
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Arg Phe Val Arg Arg Gly Pro Ile Phe Val Lys Gly Lys Gly Glu
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Leu Leu Thr Phe Phe Leu Lys Gly Arg Asp Lys Leu Ala Thr Phe
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Asp Val Ser Tyr Leu Met Ala Met Glu Lys Ser Lys Ala Thr Pro Ala
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Ala Arg Ala Ser Lys Lys Ile Leu Leu Pro Glu Pro Ser Ile Arg Ser
30 35 40

gtc atg cag aag tac ctg gag gac cgg ggc gag gtg acc ttt gag aag 256
Val Met Gln Lys Tyr Leu Glu Asp Arg Gly Glu Val Thr Phe Glu Lys
45 50 55

atc ttt tcc cag aag ctg ggg tac ctg ctc ttc cga gac ttc tgc ctg 304
Ile Phe Ser Gln Lys Leu Gly Tyr Leu Leu Phe Arg Asp Phe Cys Leu
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Asn His Leu Glu Glu Ala Arg Pro Leu Val Glu Phe Tyr Glu Glu Ile
75 80 85

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Lys Lys Tyr Glu Lys Leu Glu Thr Glu Glu Glu Arg Val Ala Arg Ser
90 95 100 105

cgg gag atc ttc gac tca tac atc atg aag gag ctg ctg gcc tgc tcg 448
Arg Glu Ile Phe Asp Ser Tyr Ile Met Lys Glu Leu Leu Ala Cys Ser
110 115 120

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tat ccc ttc tcg aag agt gcc act gag cat gtc caa ggc cac ctg ggg        496
His Pro Phe Ser Lys Ser Ala Thr Glu His Val Gln Gly His Leu Gly
                125                 130                 135

aag aag cag gtg cct ccg gat ctc ttc cag cca tac atc gaa gag att        544
Lys Lys Gln Val Pro Pro Asp Leu Phe Gln Pro Tyr Ile Glu Glu Ile
        140                 145                 150

tgt caa aac ctc cga ggg gac gtg ttc cag aaa ttc att gag agc gat        592
Cys Gln Asn Leu Arg Gly Asp Val Phe Gln Lys Phe Ile Glu Ser Asp
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aag ttc aca cgg ttt tgc cag tgg aag aat gtg gag ctc aac atc cac        640
Lys Phe Thr Arg Phe Cys Gln Trp Lys Asn Val Glu Leu Asn Ile His
170                 175                 180                 185

ctg acc atg aat gac ttc agc gtg cat cgc atc att ggg cgc ggg ggc        688
Leu Thr Met Asn Asp Phe Ser Val His Arg Ile Ile Gly Arg Gly Gly
                190                 195                 200

ttt ggc gag gtc tat ggg tgc cgg aag cgt gac aca ggc aag atg tac        736
Phe Gly Glu Val Tyr Gly Cys Arg Lys Arg Asp Thr Gly Lys Met Tyr
            205                 210                 215

gcc atg aag tgc ctg gac aaa aag cgc atc aag atg aag cag ggg gag        784
Ala Met Lys Cys Leu Asp Lys Lys Arg Ile Lys Met Lys Gln Gly Glu
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acc ctg gcc ctg aac gag cgc atc atg ctc tcg ctc gtc agc act ggg        832
Thr Leu Ala Leu Asn Glu Arg Ile Met Leu Ser Leu Val Ser Thr Gly
    235                 240                 245

gac tgc cca ttc att gtc tgc atg tca tac gcg ttc cac acg cca gac        880
Asp Cys Pro Phe Ile Val Cys Met Ser Tyr Ala Phe His Thr Pro Asp
250                 255                 260                 265

aag ctc agc ttc atc ctg gac ctc atg aac ggt ggg gac ctg cac tac        928
Lys Leu Ser Phe Ile Leu Asp Leu Met Asn Gly Gly Asp Leu His Tyr
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cac ctc tcc cag cac ggg gtc ttc tca gag gct gac atg cgc ttc tat        976
His Leu Ser Gln His Gly Val Phe Ser Glu Ala Asp Met Arg Phe Tyr
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gcg gcc gag atc atc ctg ggc ctg gag cac atg cac aac cgc ttc gtg       1024
Ala Ala Glu Ile Ile Leu Gly Leu Glu His Met His Asn Arg Phe Val
        300                 305                 310

gtc tac cgg gac ctg aag cca gcc aac atc ctt ctg gac gag cat ggc       1072
Val Tyr Arg Asp Leu Lys Pro Ala Asn Ile Leu Leu Asp Glu His Gly
    315                 320                 325

cac gtg cgg atc tcg gac ctg ggc ctg gcc tgt gac ttc tcc aag aag       1120
His Val Arg Ile Ser Asp Leu Gly Leu Ala Cys Asp Phe Ser Lys Lys
330                 335                 340                 345

aag ccc cat gcc agc gtg ggc acc cac ggg tac atg gct ccg gag gtc       1168
Lys Pro His Ala Ser Val Gly Thr His Gly Tyr Met Ala Pro Glu Val
                350                 355                 360

ctg cag aag ggc gtg gcc tac gac agc agt gcc gac tgg ttc tct ctg       1216
Leu Gln Lys Gly Val Ala Tyr Asp Ser Ser Ala Asp Trp Phe Ser Leu
            365                 370                 375

ggg tgc atg ctc ttc aag ttg ctg cgg ggg cac agc ccc ttc cgg cag       1264
Gly Cys Met Leu Phe Lys Leu Leu Arg Gly His Ser Pro Phe Arg Gln
        380                 385                 390

cac aag acc aaa gac aag cat gag atc gac cgc atg acg ctg acg atg       1312
His Lys Thr Lys Asp Lys His Glu Ile Asp Arg Met Thr Leu Thr Met
    395                 400                 405

gcc gtg gag ctg ccc gac tcc ttc tcc cct gaa cta cac tcc ctg ctg       1360
Ala Val Glu Leu Pro Asp Ser Phe Ser Pro Glu Leu His Ser Leu Leu
410                 415                 420                 425

gag ggg ttg ctg cag agg gat gtc aac cgg aga ttg ggc tgc ctg ggc       1408
Glu Gly Leu Leu Gln Arg Asp Val Asn Arg Arg Leu Gly Cys Leu Gly
                430                 435                 440
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Arg Gly Ala Gln Glu Val Lys Glu Ser Pro Phe Phe Arg Ser Leu Asp
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tgg cag atg gtc ttc ttg cag agg tac cct ccc ccg ctg atc ccc cca      1504
Trp Gln Met Val Phe Leu Gln Arg Tyr Pro Pro Pro Leu Ile Pro Pro
            460                 465                 470

cga ggg gag gtg aac gcg gcc gac gcc ttc gac att ggc tcc ttc gat      1552
Arg Gly Glu Val Asn Ala Ala Asp Ala Phe Asp Ile Gly Ser Phe Asp
    475                 480                 485

gag gag gac aca aaa gga atc aag tta ctg gac agt gat cag gag ctc      1600
Glu Glu Asp Thr Lys Gly Ile Lys Leu Leu Asp Ser Asp Gln Glu Leu
490                 495                 500                 505

tac cgc aac ttc ccc ctc acc atc tcg gag cgg tgg cag cag gag gtg      1648
Tyr Arg Asn Phe Pro Leu Thr Ile Ser Glu Arg Trp Gln Gln Glu Val
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gca gag act gtc ttc gac acc atc aac gct gag aca gac cgg ctg gag      1696
Ala Glu Thr Val Phe Asp Thr Ile Asn Ala Glu Thr Asp Arg Leu Glu
            525                 530                 535

gct cgc aag aaa gcc aag aac aag cag ctg ggc cat gag gaa gac tac      1744
Ala Arg Lys Lys Ala Lys Asn Lys Gln Leu Gly His Glu Glu Asp Tyr
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gcc ctg ggc aag gac tgc atc atg cat ggc tac atg tcc aag atg ggc      1792
Ala Leu Gly Lys Asp Cys Ile Met His Gly Tyr Met Ser Lys Met Gly
    555                 560                 565

aac ccc ttt ctg acc cag tgg cag cgg cgg tac ttc tac ctg ttc ccc      1840
Asn Pro Phe Leu Thr Gln Trp Gln Arg Arg Tyr Phe Tyr Leu Phe Pro
570                 575                 580                 585

aac cgc ctc gag tgg cgg ggc gag ggc gag gcc ccg cag agc ctg ctg      1888
Asn Arg Leu Glu Trp Arg Gly Glu Gly Glu Ala Pro Gln Ser Leu Leu
                590                 595                 600

acc atg gag gag atc cag tcg gtg gag gag acg cag atc aag gag cgc      1936
Thr Met Glu Glu Ile Gln Ser Val Glu Glu Thr Gln Ile Lys Glu Arg
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aag tgc ctg ctc ctc aag atc cgc ggt ggg aaa cag ttc att ttg cag      1984
Lys Cys Leu Leu Leu Lys Ile Arg Gly Gly Lys Gln Phe Ile Leu Gln
        620                 625                 630

tgc gat agc gac cct gag ctg gtg cag tgg aag aag gag ctg cgc gac      2032
Cys Asp Ser Asp Pro Glu Leu Val Gln Trp Lys Lys Glu Leu Arg Asp
    635                 640                 645

gcc tac cgc gag gcc cag cag ctg gtg cag cgg gtg ccc aag atg aag      2080
Ala Tyr Arg Glu Ala Gln Gln Leu Val Gln Arg Val Pro Lys Met Lys
650                 655                 660                 665

aac aag ccg cgc tcg ccc gtg gtg gag ctg agc aag gtg ccg ctg gtc      2128
Asn Lys Pro Arg Ser Pro Val Val Glu Leu Ser Lys Val Pro Leu Val
                670                 675                 680

cag cgc ggc agt gcc aac ggc ctc tga cccgcccacc cgccttttat            2175
Gln Arg Gly Ser Ala Asn Gly Leu
            685

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Leu Leu Pro Glu Pro Ser Ile Arg Ser Val Met Gln Lys Tyr Leu Glu
35 40 45

Asp Arg Gly Glu Val Thr Phe Glu Lys Ile Phe Ser Gln Lys Leu Gly
50 55 60

Tyr Leu Leu Phe Arg Asp Phe Cys Leu Asn His Leu Glu Glu Ala Arg
65 70 75 80

Pro Leu Val Glu Phe Tyr Glu Glu Ile Lys Lys Tyr Glu Lys Leu Glu
85 90 95

Thr Glu Glu Glu Arg Val Ala Arg Ser Arg Glu Ile Phe Asp Ser Tyr
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Ile Met Lys Glu Leu Leu Ala Cys Ser His Pro Phe Ser Lys Ser Ala
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Thr Glu His Val Gln Gly His Leu Gly Lys Lys Gln Val Pro Pro Asp
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Leu Phe Gln Pro Tyr Ile Glu Glu Ile Cys Gln Asn Leu Arg Gly Asp
145 150 155 160

Val Phe Gln Lys Phe Ile Glu Ser Asp Lys Phe Thr Arg Phe Cys Gln
165 170 175

Trp Lys Asn Val Glu Leu Asn Ile His Leu Thr Met Asn Asp Phe Ser
180 185 190

Val His Arg Ile Ile Gly Arg Gly Gly Phe Gly Glu Val Tyr Gly Cys
195 200 205

Arg Lys Arg Asp Thr Gly Lys Met Tyr Ala Met Lys Cys Leu Asp Lys
210 215 220

Lys Arg Ile Lys Met Lys Gln Gly Glu Thr Leu Ala Leu Asn Glu Arg
225 230 235 240

Ile Met Leu Ser Leu Val Ser Thr Gly Asp Cys Pro Phe Ile Val Cys
245 250 255

Met Ser Tyr Ala Phe His Thr Pro Asp Lys Leu Ser Phe Ile Leu Asp
260 265 270

Leu Met Asn Gly Gly Asp Leu His Tyr His Leu Ser Gln His Gly Val
275 280 285

Phe Ser Glu Ala Asp Met Arg Phe Tyr Ala Ala Glu Ile Ile Leu Gly
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Leu Glu His Met His Asn Arg Phe Val Val Tyr Arg Asp Leu Lys Pro
305 310 315 320

Ala Asn Ile Leu Leu Asp Glu His Gly His Val Arg Ile Ser Asp Leu
325 330 335

Gly Leu Ala Cys Asp Phe Ser Lys Lys Lys Pro His Ala Ser Val Gly
340 345 350

Thr His Gly Tyr Met Ala Pro Glu Val Leu Gln Lys Gly Val Ala Tyr
355 360 365

Asp Ser Ser Ala Asp Trp Phe Ser Leu Gly Cys Met Leu Phe Lys Leu
370 375 380

Leu Arg Gly His Ser Pro Phe Arg Gln His Lys Thr Lys Asp Lys His
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Glu Ile Asp Arg Met Thr Leu Thr Met Ala Val Glu Leu Pro Asp Ser
405 410 415

Phe Ser Pro Glu Leu His Ser Leu Leu Glu Gly Leu Leu Gln Arg Asp
420 425 430

Val Asn Arg Arg Leu Gly Cys Leu Gly Arg Gly Ala Gln Glu Val Lys
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Glu Ser Pro Phe Phe Arg Ser Leu Asp Trp Gln Met Val Phe Leu Gln
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Arg Tyr Pro Pro Pro Leu Ile Pro Pro Arg Gly Glu Val Asn Ala Ala
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Asp Ala Phe Asp Ile Gly Ser Phe Asp Glu Glu Asp Thr Lys Gly Ile
485 490 495

Lys Leu Leu Asp Ser Asp Gln Glu Leu Tyr Arg Asn Phe Pro Leu Thr
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Ile Ser Glu Arg Trp Gln Gln Glu Val Ala Glu Thr Val Phe Asp Thr
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Ile Asn Ala Glu Thr Asp Arg Leu Glu Ala Arg Lys Lys Ala Lys Asn
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Lys Gln Leu Gly His Glu Glu Asp Tyr Ala Leu Gly Lys Asp Cys Ile
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Met His Gly Tyr Met Ser Lys Met Gly Asn Pro Phe Leu Thr Gln Trp
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Gln Arg Arg Tyr Phe Tyr Leu Phe Pro Asn Arg Leu Glu Trp Arg Gly
580 585 590

Glu Gly Glu Ala Pro Gln Ser Leu Leu Thr Met Glu Glu Ile Gln Ser
595 600 605

Val Glu Glu Thr Gln Ile Lys Glu Arg Lys Cys Leu Leu Leu Lys Ile
610 615 620

Arg Gly Gly Lys Gln Phe Ile Leu Gln Cys Asp Ser Asp Pro Glu Leu
625 630 635 640

Val Gln Trp Lys Lys Glu Leu Arg Asp Ala Tyr Arg Glu Ala Gln Gln
645 650 655

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Ile Pro Lys Pro Leu Asn Pro Ala Leu Trp Phe Ser His Ser Met Phe
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atg ggc ttc tac ctg ctc agc ttc ctc ctg gaa cgg aag cct tgc aca 386
Met Gly Phe Tyr Leu Leu Ser Phe Leu Leu Glu Arg Lys Pro Cys Thr
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att tgt gcc ttg gtt ttc ctg gca gcc ctg ttc ctt atc tgc tat agc 434
Ile Cys Ala Leu Val Phe Leu Ala Ala Leu Phe Leu Ile Cys Tyr Ser
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Cys Trp Gly Asn Cys Phe Leu Tyr His Cys Ser Asp Ser Pro Leu Pro
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Glu Ser Ala His Asp Pro Gly Val Val Gly Thr
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Leu Leu Ser Phe Leu Leu Glu Arg Lys Pro Cys Thr Ile Cys Ala Leu
35 40 45

Val Phe Leu Ala Ala Leu Phe Leu Ile Cys Tyr Ser Cys Trp Gly Asn
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gatgtgctgg ccccggatcc agcgtcgccc acgaccgcag cagcctcgcc cagcgtctcc 240

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Met Glu Gln Pro Val Phe Leu Met Thr
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act gcc gct cag gcc atc tct ggc ttc ttc gtg tgg acg gcc ctg ctc 342
Thr Ala Ala Gln Ala Ile Ser Gly Phe Phe Val Trp Thr Ala Leu Leu
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atc aca tgc cac cag atc tac atg cac ctg cgc tgc tac agc tgc ccc 390
Ile Thr Cys His Gln Ile Tyr Met His Leu Arg Cys Tyr Ser Cys Pro
30 35 40

aac gag cag cgc tac atc gtg cgc atc ctc ttc atc gtg ccc atc tac 438
Asn Glu Gln Arg Tyr Ile Val Arg Ile Leu Phe Ile Val Pro Ile Tyr
45 50 55

gcc ttt gac tcc tgg ctc agc ctc ctc ttc ttc acc aac gac cag tac 486
Ala Phe Asp Ser Trp Leu Ser Leu Leu Phe Phe Thr Asn Asp Gln Tyr
60 65 70

tac gtg tac ttc ggc acc gtc cgc gac tgc tat gag gcc ttg gtc atc 534
Tyr Val Tyr Phe Gly Thr Val Arg Asp Cys Tyr Glu Ala Leu Val Ile
75 80 85

tat aat ttc ctg agc ctg tgc tat gag tac cta gga gga gaa agt tcc 582
Tyr Asn Phe Leu Ser Leu Cys Tyr Glu Tyr Leu Gly Gly Glu Ser Ser
90 95 100 105

atc atg tcg gag atc aga gga aaa ccc att gag tcc agc tgt atg tat 630
Ile Met Ser Glu Ile Arg Gly Lys Pro Ile Glu Ser Ser Cys Met Tyr
110 115 120

ggc acc tgc tgc ctc tgg gga aag act tat tcc atc gga ttt ctg agg 678
Gly Thr Cys Cys Leu Trp Gly Lys Thr Tyr Ser Ile Gly Phe Leu Arg
125 130 135

ttc tgc aaa cag gcc acc ctg cag ttc tgt gtg gtg aag cca ctc atg 726
Phe Cys Lys Gln Ala Thr Leu Gln Phe Cys Val Val Lys Pro Leu Met

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gac ttt gac gtc acc agt ggc tac ctc tac gtg acc atc atc tac aac      822
Asp Phe Asp Val Thr Ser Gly Tyr Leu Tyr Val Thr Ile Ile Tyr Asn
170                 175                 180                 185

atc tcc gtc agc ctg gcc ctc tac gcc ctc ttc ctc ttc tac ttc gcc      870
Ile Ser Val Ser Leu Ala Leu Tyr Ala Leu Phe Leu Phe Tyr Phe Ala
                190                 195                 200

acc cgg gag ctg ctc agc ccc tac agc ccc gtc ctc aag ttc ttc atg      918
Thr Arg Glu Leu Leu Ser Pro Tyr Ser Pro Val Leu Lys Phe Phe Met
            205                 210                 215

gtc aag tcc gtc atc ttt ctt tcc ttc tgg caa ggc atg ctc ctg gcc      966
Val Lys Ser Val Ile Phe Leu Ser Phe Trp Gln Gly Met Leu Leu Ala
        220                 225                 230

atc ctg gag aag tgt ggg gcc atc ccc aaa atc cac tcg gcc cgc gtg      1014
Ile Leu Glu Lys Cys Gly Ala Ile Pro Lys Ile His Ser Ala Arg Val
    235                 240                 245

tcg gtg ggc gag ggc acc gtg gct gcc ggc tac cag gac ttc atc atc      1062
Ser Val Gly Glu Gly Thr Val Ala Ala Gly Tyr Gln Asp Phe Ile Ile
250                 255                 260                 265

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Cys Val Glu Met Phe Phe Ala Ala Leu Ala Leu Arg His Ala Phe Thr
                270                 275                 280

tac aag gtc tat gct gac aag agg ctg gac gca caa ggc cgc tgt gcc      1158
Tyr Lys Val Tyr Ala Asp Lys Arg Leu Asp Ala Gln Gly Arg Cys Ala
            285                 290                 295

ccc atg aag agc atc tcc agc agc ctc aag gag acc atg aac ccg cac      1206
Pro Met Lys Ser Ile Ser Ser Ser Leu Lys Glu Thr Met Asn Pro His
        300                 305                 310

gac atc gtg cag gac gcc atc cac aac ttc tca cct gcc tac cag cag      1254
Asp Ile Val Gln Asp Ala Ile His Asn Phe Ser Pro Ala Tyr Gln Gln
    315                 320                 325

tac acg cag cag tcc acc ctg gag cct ggg ccc acc tgg cgt ggt ggc      1302
Tyr Thr Gln Gln Ser Thr Leu Glu Pro Gly Pro Thr Trp Arg Gly Gly
330                 335                 340                 345

gcc cac ggc ctc tcc cgc tcc cac agc ctc agt ggc gcc cgc gac aac      1350
Ala His Gly Leu Ser Arg Ser His Ser Leu Ser Gly Ala Arg Asp Asn
                350                 355                 360

gag aag act ctc ctg ctc agc tct gat gat gaa ttc tag gtgcgggctg      1399
Glu Lys Thr Leu Leu Leu Ser Ser Asp Asp Glu Phe
            365                 370

cagtggcgga agtgctggcg ccatagccac ggtcaggctg tgccccacct ccagcctcac  1459

caccaggcca ggaggcagct ggcacagtgc tcacgccgcc tttatttatt ggaccagaaa  1519

cactcacatg tcacttccag aggaacgggg gacagccagg ctcgcccatg ggccttcagg  1579

aatatttata catggcccag cctgcactgc ccgggcgagg gcagaggaca ctgggagcaa  1639

ggcttatgcc cctgctgccc gtcctgtgct gggggcatgc tgggaccagc cgcacccagg  1699

ccccaatgct tgtgtgtgga ccagcggctg cagccttcta gcccctcctc cccgcgagac  1759

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ctgggctctt cccgcctgca tccctccccc gtccaccttt gtccagtgct agattcacct  1879

caccccgggc aggagtgggg atgtgggcgc tctgtggtcc tcccctcctg acccaggcct  1939

ctgtggcatg ctgcaaggat cagagccaga caccaggagt cacaggcccc acccaggaag  1999

ggcattcagg gcccctgggc accgcttctg ttgaagcagg ggcttctggg cccctgggta  2059
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tccccacctg tcgtggccac acctctgcct gcctcatgcc ccttcccccc ggcctaccaa 2119
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<400> 14

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Gly Phe Phe Val Trp Thr Ala Leu Leu Ile Thr Cys His Gln Ile Tyr
20 25 30

Met His Leu Arg Cys Tyr Ser Cys Pro Asn Glu Gln Arg Tyr Ile Val
35 40 45

Arg Ile Leu Phe Ile Val Pro Ile Tyr Ala Phe Asp Ser Trp Leu Ser
50 55 60

Leu Leu Phe Phe Thr Asn Asp Gln Tyr Tyr Val Tyr Phe Gly Thr Val
65 70 75 80

Arg Asp Cys Tyr Glu Ala Leu Val Ile Tyr Asn Phe Leu Ser Leu Cys
85 90 95

Tyr Glu Tyr Leu Gly Gly Glu Ser Ser Ile Met Ser Glu Ile Arg Gly
100 105 110

Lys Pro Ile Glu Ser Ser Cys Met Tyr Gly Thr Cys Cys Leu Trp Gly
115 120 125

Lys Thr Tyr Ser Ile Gly Phe Leu Arg Phe Cys Lys Gln Ala Thr Leu
130 135 140

Gln Phe Cys Val Val Lys Pro Leu Met Ala Val Ser Thr Val Val Leu
145 150 155 160

Gln Ala Phe Gly Lys Tyr Arg Asp Gly Asp Phe Asp Val Thr Ser Gly
165 170 175

Tyr Leu Tyr Val Thr Ile Ile Tyr Asn Ile Ser Val Ser Leu Ala Leu
180 185 190

Tyr Ala Leu Phe Leu Phe Tyr Phe Ala Thr Arg Glu Leu Leu Ser Pro
195 200 205

Tyr Ser Pro Val Leu Lys Phe Phe Met Val Lys Ser Val Ile Phe Leu
210 215 220

Ser Phe Trp Gln Gly Met Leu Leu Ala Ile Leu Glu Lys Cys Gly Ala
225 230 235 240

Ile Pro Lys Ile His Ser Ala Arg Val Ser Val Gly Glu Gly Thr Val
245 250 255

Ala Ala Gly Tyr Gln Asp Phe Ile Ile Cys Val Glu Met Phe Phe Ala
260 265 270

Ala Leu Ala Leu Arg His Ala Phe Thr Tyr Lys Val Tyr Ala Asp Lys
275 280 285

Arg Leu Asp Ala Gln Gly Arg Cys Ala Pro Met Lys Ser Ile Ser Ser
290 295 300

Ser Leu Lys Glu Thr Met Asn Pro His Asp Ile Val Gln Asp Ala Ile
305 310 315 320

His Asn Phe Ser Pro Ala Tyr Gln Gln Tyr Thr Gln Gln Ser Thr Leu
325 330 335

Glu Pro Gly Pro Thr Trp Arg Gly Gly Ala His Gly Leu Ser Arg Ser
340 345 350

His Ser Leu Ser Gly Ala Arg Asp Asn Glu Lys Thr Leu Leu Leu Ser
355 360 365

Ser Asp Asp Glu Phe
370

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<222> (41)..(751)
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Cys Thr Lys Cys Ile Lys Tyr Leu Leu Phe Val Phe Asn Phe Val Phe
                10                  15                  20

tgg ctg gct gga ggc gtg atc ctg ggt gtg gcc ctg tgg ctc cgc cat       151
Trp Leu Ala Gly Gly Val Ile Leu Gly Val Ala Leu Trp Leu Arg His
            25                  30                  35

gac ccg cag acc acc aac ctc ctg tat ctg gag ctg gga gac aag ccc       199
Asp Pro Gln Thr Thr Asn Leu Leu Tyr Leu Glu Leu Gly Asp Lys Pro
        40                  45                  50

gcg ccc aac acc ttc tat gta ggc atc tac atc ctc atc gct gtg ggc       247
Ala Pro Asn Thr Phe Tyr Val Gly Ile Tyr Ile Leu Ile Ala Val Gly
    55                  60                  65

gct gtc atg atg ttc gtt ggc ttc ctg ggc tgc tac ggg gcc atc cag       295
Ala Val Met Met Phe Val Gly Phe Leu Gly Cys Tyr Gly Ala Ile Gln
70                  75                  80                  85

gaa tcc cag tgc ctg ctg ggg acg ttc ttc acc tgc ctg gtc atc ctg       343
Glu Ser Gln Cys Leu Leu Gly Thr Phe Phe Thr Cys Leu Val Ile Leu
                90                  95                  100

ttt gcc tgt gag gtg gcc gcc ggc atc tgg ggc ttt gtc aac aag gac       391
Phe Ala Cys Glu Val Ala Ala Gly Ile Trp Gly Phe Val Asn Lys Asp
            105                 110                 115

cag atc gcc aag gat gtg aag cag ttc tat gac cag gcc cta cag cag       439
Gln Ile Ala Lys Asp Val Lys Gln Phe Tyr Asp Gln Ala Leu Gln Gln
        120                 125                 130

gcc gtg gtg gat gat gac gcc aac aac gcc aag gct gtg gtg aag acc       487
Ala Val Val Asp Asp Asp Ala Asn Asn Ala Lys Ala Val Val Lys Thr
    135                 140                 145

ttc cac gag acg ctt gac tgc tgt ggc tcc agc aca ctg act gct ttg       535
Phe His Glu Thr Leu Asp Cys Cys Gly Ser Ser Thr Leu Thr Ala Leu
150                 155                 160                 165

acc acc tca gtg ctc aag aac aat ttg tgt ccc tcg ggc agc aac atc       583
Thr Thr Ser Val Leu Lys Asn Asn Leu Cys Pro Ser Gly Ser Asn Ile
                170                 175                 180

atc agc aac ctc ttc aag gag gac tgc cac cag aag atc gat gac ctc       631
Ile Ser Asn Leu Phe Lys Glu Asp Cys His Gln Lys Ile Asp Asp Leu
            185                 190                 195

ttc tcc ggg aag ctg tac ctc atc ggc att gct gcc atc gtg gtc gct       679
Phe Ser Gly Lys Leu Tyr Leu Ile Gly Ile Ala Ala Ile Val Val Ala
        200                 205                 210

gtg atc atg atc ttc gag atg atc ctg agc atg gtg ctg tgc tgt ggc       727
Val Ile Met Ile Phe Glu Met Ile Leu Ser Met Val Leu Cys Cys Gly
    215                 220                 225

atc cgg aac agc tcc gtg tac tga ggccccgcag ctctggccac agggacctct      781
Ile Arg Asn Ser Ser Val Tyr
230                 235

gcagtgcccc ctaagtgacc cggacacttc cgaggggggcc atcaccgcct gtgtatataa     841

cgtttccggt attactctgc tacacgtagc ctttttactt ttggggtttt gtttttgttc     901

tgaactttcc tgttaccttt tcagggctga cgtcacatgt aggtggcgtg tatgagtgga     961

gacgggcctg ggtcttgggg actggagggc aggggtcctt ctgccctggg gtcccagggt    1021

gctctgcctg ctcagccagg cctctcctgg gagccactcg cccagagact cagcttggcc    1081
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aacttggggg gctgtgtcca cccagcccgc ccgtcctgtg ggctgcacag ctcaccttgt 1141
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cctttctaac acgtcgcctt caactgtaat cacaacatcc tgactccgtc atttaataaa 1261
gaaggaacat caggcatgct aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1321
aaaaaaaaaa a 1332

<210> 16
<211> 236
<212> PRT
<213> Homo sapiens

<400> 16

Met Gly Val Glu Gly Cys Thr Lys Cys Ile Lys Tyr Leu Leu Phe Val
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Phe Asn Phe Val Phe Trp Leu Ala Gly Gly Val Ile Leu Gly Val Ala
20 25 30

Leu Trp Leu Arg His Asp Pro Gln Thr Thr Asn Leu Leu Tyr Leu Glu
35 40 45

Leu Gly Asp Lys Pro Ala Pro Asn Thr Phe Tyr Val Gly Ile Tyr Ile
50 55 60

Leu Ile Ala Val Gly Ala Val Met Met Phe Val Gly Phe Leu Gly Cys
65 70 75 80

Tyr Gly Ala Ile Gln Glu Ser Gln Cys Leu Leu Gly Thr Phe Phe Thr
85 90 95

Cys Leu Val Ile Leu Phe Ala Cys Glu Val Ala Ala Gly Ile Trp Gly
100 105 110

Phe Val Asn Lys Asp Gln Ile Ala Lys Asp Val Lys Gln Phe Tyr Asp
115 120 125

Gln Ala Leu Gln Gln Ala Val Val Asp Asp Asp Ala Asn Asn Ala Lys
130 135 140

Ala Val Val Lys Thr Phe His Glu Thr Leu Asp Cys Cys Gly Ser Ser
145 150 155 160

Thr Leu Thr Ala Leu Thr Thr Ser Val Leu Lys Asn Asn Leu Cys Pro
165 170 175

Ser Gly Ser Asn Ile Ile Ser Asn Leu Phe Lys Glu Asp Cys His Gln
180 185 190

Lys Ile Asp Asp Leu Phe Ser Gly Lys Leu Tyr Leu Ile Gly Ile Ala
195 200 205

Ala Ile Val Val Ala Val Ile Met Ile Phe Glu Met Ile Leu Ser Met
210 215 220

Val Leu Cys Cys Gly Ile Arg Asn Ser Ser Val Tyr
225 230 235

<210> 17
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<212> DNA
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cgcgcccccc agtcccgcac ccgttcggcc caggctaagt tagccctcac c atg ccg      117
                                                          Met Pro
                                                            1

gtc aaa gga ggc acc aag tgc atc aaa tac ctg ctg ttc gga ttt aac      165
Val Lys Gly Gly Thr Lys Cys Ile Lys Tyr Leu Leu Phe Gly Phe Asn
        5                  10                  15

ttc atc ttc tgg ctt gcc ggg att gct gtc ctt gcc att gga cta tgg      213
Phe Ile Phe Trp Leu Ala Gly Ile Ala Val Leu Ala Ile Gly Leu Trp
    20                  25                  30

ctc cga ttc gac tct cag acc aag agc atc ttc gag caa gaa act aat      261
Leu Arg Phe Asp Ser Gln Thr Lys Ser Ile Phe Glu Gln Glu Thr Asn
35                  40                  45                  50

aat aat aat tcc agc ttc tac aca gga gtc tat att ctg atc gga gcc      309
Asn Asn Asn Ser Ser Phe Tyr Thr Gly Val Tyr Ile Leu Ile Gly Ala
                55                  60                  65

ggc gcc ctc atg atg ctg gtg ggc ttc ctg ggc tgc tgc ggg gct gtg      357
Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly Ala Val
            70                  75                  80

cag gag tcc cag tgc atg ctg gga ctg ttc ttc ggc ttc ctc ttg gtg      405
Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu Leu Val
        85                  90                  95

ata ttc gcc att gaa ata gct gcg gcc atc tgg gga tat tcc cac aag      453
Ile Phe Ala Ile Glu Ile Ala Ala Ala Ile Trp Gly Tyr Ser His Lys
    100                 105                 110

gat gag gtg att aag gaa gtc cag gag ttt tac aag gac acc tac aac      501
Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr Tyr Asn
115                 120                 125                 130

aag ctg aaa acc aag gat gag ccc cag cgg gaa acg ctg aaa gcc atc      549
Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys Ala Ile
                135                 140                 145

cac tat gcg ttg aac tgc tgt ggt ttg gct ggg ggc gtg gaa cag ttt      597
His Tyr Ala Leu Asn Cys Cys Gly Leu Ala Gly Gly Val Glu Gln Phe
            150                 155                 160

atc tca gac atc tgc ccc aag aag gac gta ctc gaa acc ttc acc gtg      645
Ile Ser Asp Ile Cys Pro Lys Lys Asp Val Leu Glu Thr Phe Thr Val
        165                 170                 175

aag tcc tgt cct gat gcc atc aaa gag gtc ttc gac aat aaa ttc cac      693
Lys Ser Cys Pro Asp Ala Ile Lys Glu Val Phe Asp Asn Lys Phe His
    180                 185                 190

atc atc ggc gca gtg ggc atc ggc att gcc gtg gtc atg ata ttt ggc      741
Ile Ile Gly Ala Val Gly Ile Gly Ile Ala Val Val Met Ile Phe Gly
195                 200                 205                 210

atg atc ttc agt atg atc ttg tgc tgt gct atc cgc agg aac cgc gag      789
Met Ile Phe Ser Met Ile Leu Cys Cys Ala Ile Arg Arg Asn Arg Glu
                215                 220                 225

atg gtc tag agtcagctta catccctgag caggaaagtt tacccatgaa               838
Met Val

gattggtggg atttttttgtt tgtttgtttt gttttgtttg ttgtttgttg tttgtttttt    898

tgccactaat tttagtattc attctgcatt gctagataaa agctgaagtt actttatgtt    958

tgtcttttaa tgcttcattc aatattgaca tttgtagttg agcgggggggt ttggtttgct   1018
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ttggtttata ttttttcagt tgtttgtttt tgcttgttat attaagcaga aatcctgcaa 1078

tgaaaggtac tatatttgct agactctaga caagatattg tacataaaag aatttttttg 1138

tctttaaata gatacaaatg tctatcaact ttaatcaagt tgtaacttat attgaagaca 1198

atttgataca taataaaaaa ttatgacaat gtcaaaaaaa aaaaaaaa 1246

<210> 18
<211> 228
<212> PRT
<213> Homo sapiens

<400> 18

Met Pro Val Lys Gly Gly Thr Lys Cys Ile Lys Tyr Leu Leu Phe Gly
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Phe Asn Phe Ile Phe Trp Leu Ala Gly Ile Ala Val Leu Ala Ile Gly
20 25 30

Leu Trp Leu Arg Phe Asp Ser Gln Thr Lys Ser Ile Phe Glu Gln Glu
35 40 45

Thr Asn Asn Asn Asn Ser Ser Phe Tyr Thr Gly Val Tyr Ile Leu Ile
50 55 60

Gly Ala Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly
65 70 75 80

Ala Val Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu
85 90 95

Leu Val Ile Phe Ala Ile Glu Ile Ala Ala Ala Ile Trp Gly Tyr Ser
100 105 110

His Lys Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr
115 120 125

Tyr Asn Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys
130 135 140

Ala Ile His Tyr Ala Leu Asn Cys Cys Gly Leu Ala Gly Gly Val Glu
145 150 155 160

Gln Phe Ile Ser Asp Ile Cys Pro Lys Lys Asp Val Leu Glu Thr Phe
165 170 175

Thr Val Lys Ser Cys Pro Asp Ala Ile Lys Glu Val Phe Asp Asn Lys
180 185 190

Phe His Ile Ile Gly Ala Val Gly Ile Gly Ile Ala Val Val Met Ile
195 200 205

Phe Gly Met Ile Phe Ser Met Ile Leu Cys Cys Ala Ile Arg Arg Asn
210 215 220

Arg Glu Met Val
225

<210> 19
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<400> 19

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ctgtccccga gagagagtgc cctggcagct gtcggctgga aggaactggt ctgctcacac    180

ttgctggctt gcgcatcagg actggcttta tctcctgact cacggtgcaa aggtgcactc    240

tgcgaacgtt aagtccgtcc ccagcgcttg gaatcctacg gcccccacag ccggatcccc    300

tcagccttcc aggtcctcaa ctcccgtgga cgctgaaca atg gcc tcc atg ggg       354
                                          Met Ala Ser Met Gly
                                          1               5

cta cag gta atg ggc atc gcg ctg gcc gtc ctg ggc tgg ctg gcc gtc      402
Leu Gln Val Met Gly Ile Ala Leu Ala Val Leu Gly Trp Leu Ala Val
                10                  15                  20

atg ctg tgc tgc gcg ctg ccc atg tgg cgc gtg acg gcc ttc atc ggc      450
Met Leu Cys Cys Ala Leu Pro Met Trp Arg Val Thr Ala Phe Ile Gly
            25                  30                  35

agc aac att gtc acc tcg cag acc atc tgg gag ggc cta tgg atg aac      498
Ser Asn Ile Val Thr Ser Gln Thr Ile Trp Glu Gly Leu Trp Met Asn
        40                  45                  50

tgc gtg gtg cag agc acc ggc cag atg cag tgc aag gtg tac gac tcg      546
Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys Val Tyr Asp Ser
    55                  60                  65

ctg ctg gca ctg ccg cag gac ctg cag gcg gcc cgc gcc ctc gtc atc      594
Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg Ala Leu Val Ile
70                  75                  80                  85

atc agc atc atc gtg gct gct ctg ggc gtg ctg ctg tcc gtg gtg ggg      642
Ile Ser Ile Ile Val Ala Ala Leu Gly Val Leu Leu Ser Val Val Gly
                90                  95                  100

ggc aag tgt acc aac tgc ctg gag gat gaa agc gcc aag gcc aag acc      690
Gly Lys Cys Thr Asn Cys Leu Glu Asp Glu Ser Ala Lys Ala Lys Thr
            105                 110                 115

atg atc gtg gcg ggc gtg gtg ttc ctg ttg gcc ggc ctt atg gtg ata      738
Met Ile Val Ala Gly Val Val Phe Leu Leu Ala Gly Leu Met Val Ile
        120                 125                 130

gtg ccg gtg tcc tgg acg gcc cac aac atc atc caa gac ttc tac aat      786
Val Pro Val Ser Trp Thr Ala His Asn Ile Ile Gln Asp Phe Tyr Asn
    135                 140                 145

ccg ctg gtg gcc tcc ggg cag aag cgg gag atg ggt gcc tcg ctc tac      834
Pro Leu Val Ala Ser Gly Gln Lys Arg Glu Met Gly Ala Ser Leu Tyr
150                 155                 160                 165

gtc ggc tgg gcc gcc tcc ggc ctg ctg ctc ctt ggc ggg ggg ctg ctt      882
Val Gly Trp Ala Ala Ser Gly Leu Leu Leu Leu Gly Gly Gly Leu Leu
                170                 175                 180

tgc tgc aac tgt cca ccc cgc aca gac aag cct tac tcc gcc aag tat      930
Cys Cys Asn Cys Pro Pro Arg Thr Asp Lys Pro Tyr Ser Ala Lys Tyr
            185                 190                 195

tct gct gcc cgc tct gct gct gcc agc aac tac gtg taa ggtgccacgg       979
Ser Ala Ala Arg Ser Ala Ala Ala Ser Asn Tyr Val
        200                 205

ctccactctg ttcctctctg ctttgttctt ccctggactg agctcagcgc aggctgtgac   1039

cccaggaggg ccctgccacg ggccactggc tgctggggac tggggactgg gcagagactg   1099

agccaggcag gaaggcagca gccttcagcc tctctggccc actcggacaa cttcccaagg   1159

ccgcctcctg ctagcaagaa cagagtccac cctcctctgg atattgggga gggacggaag   1219
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<212> PRT
<213> Homo sapiens

<400> 20

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Gly Trp Leu Ala Val Met Leu Cys Cys Ala Leu Pro Met Trp Arg Val
20 25 30

Thr Ala Phe Ile Gly Ser Asn Ile Val Thr Ser Gln Thr Ile Trp Glu
35 40 45

Gly Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys
50 55 60

Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala
65 70 75 80

Arg Ala Leu Val Ile Ile Ser Ile Ile Val Ala Ala Leu Gly Val Leu
85 90 95

Leu Ser Val Val Gly Gly Lys Cys Thr Asn Cys Leu Glu Asp Glu Ser
100 105 110

Ala Lys Ala Lys Thr Met Ile Val Ala Gly Val Val Phe Leu Leu Ala
115 120 125

Gly Leu Met Val Ile Val Pro Val Ser Trp Thr Ala His Asn Ile Ile
130 135 140

Gln Asp Phe Tyr Asn Pro Leu Val Ala Ser Gly Gln Lys Arg Glu Met
145 150 155 160

Gly Ala Ser Leu Tyr Val Gly Trp Ala Ala Ser Gly Leu Leu Leu Leu
165 170 175

Gly Gly Gly Leu Leu Cys Cys Asn Cys Pro Pro Arg Thr Asp Lys Pro
180 185 190

Tyr Ser Ala Lys Tyr Ser Ala Ala Arg Ser Ala Ala Ala Ser Asn Tyr
195 200 205

Val

<210> 21
<211> 1225
<212> DNA
<213> Homo sapiens

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<222> (237)..(962)
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gaagggacag ccctgggtct aggggagaga gtccctgagt gtgagacccg ccttccccgg 180

tcccagcccc tcccagttcc cccagggacg gccacttcct ggtccccgac gcaacc atg 239
Met
1

gct gaa gaa caa ccg cag gtc gaa ttg ttc gtg aag gct ggc agt gat 287
Ala Glu Glu Gln Pro Gln Val Glu Leu Phe Val Lys Ala Gly Ser Asp
5 10 15

ggg gcc aag att ggg aac tgc cca ttc tcc cag aga ctg ttc atg gta 335
Gly Ala Lys Ile Gly Asn Cys Pro Phe Ser Gln Arg Leu Phe Met Val
20 25 30

ctg tgg ctc aag gga gtc acc ttc aat gtt acc acc gtt gac acc aaa 383
Leu Trp Leu Lys Gly Val Thr Phe Asn Val Thr Thr Val Asp Thr Lys
35 40 45

agg cgg acc gag aca gtg cag aag ctg tgc cca ggg ggg cag ctc cca 431
Arg Arg Thr Glu Thr Val Gln Lys Leu Cys Pro Gly Gly Gln Leu Pro
50 55 60 65

ttc ctg ctg tat ggc act gaa gtg cac aca gac acc aac aag att gag 479
Phe Leu Leu Tyr Gly Thr Glu Val His Thr Asp Thr Asn Lys Ile Glu
70 75 80

gaa ttt ctg gag gca gtg ctg tgc cct ccc agg tac ccc aag ctg gca 527
Glu Phe Leu Glu Ala Val Leu Cys Pro Pro Arg Tyr Pro Lys Leu Ala
85 90 95

gct ctg aac cct gag tcc aac aca gct ggg ctg gac ata ttt gcc aaa 575
Ala Leu Asn Pro Glu Ser Asn Thr Ala Gly Leu Asp Ile Phe Ala Lys
100 105 110

ttt tct gcc tac atc aag aat tca aac cca gca ctc aat gac aat ctg 623
Phe Ser Ala Tyr Ile Lys Asn Ser Asn Pro Ala Leu Asn Asp Asn Leu
115 120 125

gag aag gga ctc ctg aaa gcc ctg aag gtt tta gac aat tac tta aca 671
Glu Lys Gly Leu Leu Lys Ala Leu Lys Val Leu Asp Asn Tyr Leu Thr
130 135 140 145

tcc ccc ctc cca gaa gaa gtg gat gaa acc agt gct gaa gat gaa ggt 719
Ser Pro Leu Pro Glu Glu Val Asp Glu Thr Ser Ala Glu Asp Glu Gly
150 155 160

gtc tct cag agg aag ttt ttg gat ggc aac gag ctc acc ctg gct gac 767
Val Ser Gln Arg Lys Phe Leu Asp Gly Asn Glu Leu Thr Leu Ala Asp
165 170 175

tgc aac ctg ttg cca aag tta cac ata gta cag gtg gtg tgt aag aag 815
Cys Asn Leu Leu Pro Lys Leu His Ile Val Gln Val Val Cys Lys Lys
180 185 190

tac cgg gga ttc acc atc ccc gag gcc ttc cgg gga gtg cat cgg tac 863
Tyr Arg Gly Phe Thr Ile Pro Glu Ala Phe Arg Gly Val His Arg Tyr
195 200 205

ttg agc aat gcc tac gcc cgg gaa gaa ttc gct tcc acc tgt cca gat 911
Leu Ser Asn Ala Tyr Ala Arg Glu Glu Phe Ala Ser Thr Cys Pro Asp

210 215 220 225

gat gag gag atc gag ctc gcc tat gag caa gtg gca aag gcc ctc aaa 959
Asp Glu Glu Ile Glu Leu Ala Tyr Glu Gln Val Ala Lys Ala Leu Lys
230 235 240

taa gcccctcctg ggactccctc aacccccctcc attttctcca caaaggccct 1012

ggtggtttcc acattgctac ccaatggaca cactccaaaa tggccagtgg gcagggaatc 1072

ctggagcact tgttccggga tggtgtggtg gaagagggga tgagggaaag aaatgggggg 1132

cctgggtcag atttttattg tggggtgggg tgagtaggac aacatatttc agtaataaaa 1192

tacagaataa aaatcaagtg tttttaaaaa aaa 1225

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<213> Homo sapiens

<400> 22

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Asp Gly Ala Lys Ile Gly Asn Cys Pro Phe Ser Gln Arg Leu Phe Met
20 25 30

Val Leu Trp Leu Lys Gly Val Thr Phe Asn Val Thr Thr Val Asp Thr
35 40 45

Lys Arg Arg Thr Glu Thr Val Gln Lys Leu Cys Pro Gly Gly Gln Leu
50 55 60

Pro Phe Leu Leu Tyr Gly Thr Glu Val His Thr Asp Thr Asn Lys Ile
65 70 75 80

Glu Glu Phe Leu Glu Ala Val Leu Cys Pro Pro Arg Tyr Pro Lys Leu
85 90 95

Ala Ala Leu Asn Pro Glu Ser Asn Thr Ala Gly Leu Asp Ile Phe Ala
100 105 110

Lys Phe Ser Ala Tyr Ile Lys Asn Ser Asn Pro Ala Leu Asn Asp Asn
115 120 125

Leu Glu Lys Gly Leu Leu Lys Ala Leu Lys Val Leu Asp Asn Tyr Leu
130 135 140

Thr Ser Pro Leu Pro Glu Glu Val Asp Glu Thr Ser Ala Glu Asp Glu
145 150 155 160

Gly Val Ser Gln Arg Lys Phe Leu Asp Gly Asn Glu Leu Thr Leu Ala
165 170 175

Asp Cys Asn Leu Leu Pro Lys Leu His Ile Val Gln Val Val Cys Lys
180 185 190

Lys Tyr Arg Gly Phe Thr Ile Pro Glu Ala Phe Arg Gly Val His Arg
195 200 205

Tyr Leu Ser Asn Ala Tyr Ala Arg Glu Glu Phe Ala Ser Thr Cys Pro
210 215 220

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Asp Asp Glu Glu Ile Glu Leu Ala Tyr Glu Gln Val Ala Lys Ala Leu
225                 230                 235                 240

Lys
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aggtgctgcc aag atg ctc cag ggc acc tgc tcc gtg ctc ctg ctc tgg          109
               Met Leu Gln Gly Thr Cys Ser Val Leu Leu Leu Trp
               1               5                  10

gga atc ctg ggg gcc atc cag gcc cag cag cag gag gtc atc tcg ccg         157
Gly Ile Leu Gly Ala Ile Gln Ala Gln Gln Gln Glu Val Ile Ser Pro
        15                  20                  25

gac act acc gag aga aac aac aac tgc cca gag aag acc gac tgc ccc         205
Asp Thr Thr Glu Arg Asn Asn Asn Cys Pro Glu Lys Thr Asp Cys Pro
    30                  35                  40

atc cac gtg tac ttc gtg ctg gac acc tcg gag agc gtc acc atg cag         253
Ile His Val Tyr Phe Val Leu Asp Thr Ser Glu Ser Val Thr Met Gln
45                  50                  55                  60

tcc ccc acg gac atc ctg ctc ttc cac atg aag cag ttc gtg ccg cag         301
Ser Pro Thr Asp Ile Leu Leu Phe His Met Lys Gln Phe Val Pro Gln
                65                  70                  75

ttc atc agc cag ctg cag aac gag ttc tac ctg gac cag gtg gcg ctg         349
Phe Ile Ser Gln Leu Gln Asn Glu Phe Tyr Leu Asp Gln Val Ala Leu
            80                  85                  90

agc tgg cgc tac ggc ggc ctg cac ttc tct gac cag gtg gag gtg ttc         397
Ser Trp Arg Tyr Gly Gly Leu His Phe Ser Asp Gln Val Glu Val Phe
        95                  100                 105

agc cca ccg ggc agc gac cgg gcc tcc ttc atc aag aac ctg cag ggc         445
Ser Pro Pro Gly Ser Asp Arg Ala Ser Phe Ile Lys Asn Leu Gln Gly
    110                 115                 120

atc agc tcc ttc cgc cgc ggc acc ttc acc gac tgc gcg ctg gcc aac         493
Ile Ser Ser Phe Arg Arg Gly Thr Phe Thr Asp Cys Ala Leu Ala Asn
125                 130                 135                 140

atg acg gag cag atc cgg cag gac cgc agc aag ggc acc gtc cac ttc         541
Met Thr Glu Gln Ile Arg Gln Asp Arg Ser Lys Gly Thr Val His Phe
                145                 150                 155

gcc gtg gtc atc acc gac ggc cac gtc acc ggc agc ccc tgc ggg ggc         589
Ala Val Val Ile Thr Asp Gly His Val Thr Gly Ser Pro Cys Gly Gly
            160                 165                 170

atc aag ctg cag gcc gag cgg gcc cgc gag gag ggc atc cgg ctc ttc         637
Ile Lys Leu Gln Ala Glu Arg Ala Arg Glu Glu Gly Ile Arg Leu Phe
        175                 180                 185

gcc gtg gcc ccc aac cag aac ctg aag gag cag ggc ctg cgg gac atc         685
Ala Val Ala Pro Asn Gln Asn Leu Lys Glu Gln Gly Leu Arg Asp Ile
    190                 195                 200

gcc agc acg ccg cac gag ctc tac cgc aac gac tac gcc acc atg ctg         733
Ala Ser Thr Pro His Glu Leu Tyr Arg Asn Asp Tyr Ala Thr Met Leu
205                 210                 215                 220

ccc gac tcc acc gag atc aac cag gac acc atc aac cgc atc atc aag         781
Pro Asp Ser Thr Glu Ile Asn Gln Asp Thr Ile Asn Arg Ile Ile Lys
                225                 230                 235
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gtc atg aaa cac gaa gcc tac gga gag tgc tac aag gtg agc tgc ctg      829
Val Met Lys His Glu Ala Tyr Gly Glu Cys Tyr Lys Val Ser Cys Leu
            240                 245                 250

gaa atc cct ggg ccc tct ggg ccc aag ggc tac cgt gga cag aag ggt      877
Glu Ile Pro Gly Pro Ser Gly Pro Lys Gly Tyr Arg Gly Gln Lys Gly
        255                 260                 265

gcc aag ggc aac atg ggt gag ccg gga gag cct ggc cag aag gga aga      925
Ala Lys Gly Asn Met Gly Glu Pro Gly Glu Pro Gly Gln Lys Gly Arg
    270                 275                 280

cag gga gac ccg ggc atc gaa ggc ccc att gga ttc cca gga ccc aag      973
Gln Gly Asp Pro Gly Ile Glu Gly Pro Ile Gly Phe Pro Gly Pro Lys
285                 290                 295                 300

ggc gtt cct ggc ttc aaa gga gag aag ggt gaa ttt gga gcc gac ggt     1021
Gly Val Pro Gly Phe Lys Gly Glu Lys Gly Glu Phe Gly Ala Asp Gly
                305                 310                 315

cgc aag ggg gcc cct ggc ctg gct ggc aag aac ggg acc gat gga cag     1069
Arg Lys Gly Ala Pro Gly Leu Ala Gly Lys Asn Gly Thr Asp Gly Gln
            320                 325                 330

aag ggc aag ctg ggg cgc atc gga cct cct ggc tgc aag gga gac cct     1117
Lys Gly Lys Leu Gly Arg Ile Gly Pro Pro Gly Cys Lys Gly Asp Pro
        335                 340                 345

gga aac cgg ggc ccc gac ggt tac ccg ggg gaa gca ggg agt cca ggg     1165
Gly Asn Arg Gly Pro Asp Gly Tyr Pro Gly Glu Ala Gly Ser Pro Gly
    350                 355                 360

gag cga gga gac caa ggc ggc aag ggg gac cct ggc cgc cca gga cgc     1213
Glu Arg Gly Asp Gln Gly Gly Lys Gly Asp Pro Gly Arg Pro Gly Arg
365                 370                 375                 380

aga ggg ccc ccg gga gaa atc ggg gcc aag gga agc aag ggg tat caa     1261
Arg Gly Pro Pro Gly Glu Ile Gly Ala Lys Gly Ser Lys Gly Tyr Gln
                385                 390                 395

ggc aac aat gga gcc cca gga agt cct ggt gtg aaa gga gcc aag ggc     1309
Gly Asn Asn Gly Ala Pro Gly Ser Pro Gly Val Lys Gly Ala Lys Gly
            400                 405                 410

ggg cct ggg ccc cgc gga ccc aaa ggc gag ccg ggg cgc agg gga gac     1357
Gly Pro Gly Pro Arg Gly Pro Lys Gly Glu Pro Gly Arg Arg Gly Asp
        415                 420                 425

ccc ggc acc aag ggc agc cca ggc agc gat ggc ccc aag ggg gag aag     1405
Pro Gly Thr Lys Gly Ser Pro Gly Ser Asp Gly Pro Lys Gly Glu Lys
    430                 435                 440

ggg gac cct ggc cct gag ggc ccc cgc ggc ctg gct gga gag gtt ggc     1453
Gly Asp Pro Gly Pro Glu Gly Pro Arg Gly Leu Ala Gly Glu Val Gly
445                 450                 455                 460

aac aaa gga gcc aag gga gac cga ggc ttg cct gga ccc aga ggc ccc     1501
Asn Lys Gly Ala Lys Gly Asp Arg Gly Leu Pro Gly Pro Arg Gly Pro
                465                 470                 475

cag gga gct ctt ggg gag ccc gga aag cag gga tct cgg gga gac ccc     1549
Gln Gly Ala Leu Gly Glu Pro Gly Lys Gln Gly Ser Arg Gly Asp Pro
            480                 485                 490

ggt gat gca gga ccc cgt gga gac tca gga cag cca ggc ccc aag gga     1597
Gly Asp Ala Gly Pro Arg Gly Asp Ser Gly Gln Pro Gly Pro Lys Gly
        495                 500                 505

gac ccc ggc agg cct gga ttc agc tac cca gga ccc cga gga gca ccc     1645
Asp Pro Gly Arg Pro Gly Phe Ser Tyr Pro Gly Pro Arg Gly Ala Pro
    510                 515                 520

gga gaa aaa ggc gag ccc ggc cca cgc ggc ccc gag gga ggc cga ggc     1693
Gly Glu Lys Gly Glu Pro Gly Pro Arg Gly Pro Glu Gly Gly Arg Gly
525                 530                 535                 540

gac ttt ggc ttg aaa gga gaa cct ggg agg aaa gga gag aaa gga gag     1741
Asp Phe Gly Leu Lys Gly Glu Pro Gly Arg Lys Gly Glu Lys Gly Glu
                545                 550                 555
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cct gcg gat cct ggt ccc cct ggt gag cca ggc cct cgg ggg cca aga      1789
Pro Ala Asp Pro Gly Pro Pro Gly Glu Pro Gly Pro Arg Gly Pro Arg
            560                 565                 570

gga gtc cca gga ccc gag ggt gag ccc ggc ccc cct gga gac ccc ggt      1837
Gly Val Pro Gly Pro Glu Gly Glu Pro Gly Pro Pro Gly Asp Pro Gly
        575                 580                 585

ctc acg gag tgt gac gtc atg acc tac gtg agg gag acc tgc ggg tgc      1885
Leu Thr Glu Cys Asp Val Met Thr Tyr Val Arg Glu Thr Cys Gly Cys
    590                 595                 600

tgc gac tgt gag aag cgc tgt ggc gcc ctg gac gtg gtc ttc gtc atc      1933
Cys Asp Cys Glu Lys Arg Cys Gly Ala Leu Asp Val Val Phe Val Ile
605                 610                 615                 620

gac agc tcc gag agc att ggg tac acc aac ttc aca ctg gag aag aac      1981
Asp Ser Ser Glu Ser Ile Gly Tyr Thr Asn Phe Thr Leu Glu Lys Asn
                625                 630                 635

ttc gtc atc aac gtg gtc aac agg ctg ggt gcc atc gct aag gac ccc      2029
Phe Val Ile Asn Val Val Asn Arg Leu Gly Ala Ile Ala Lys Asp Pro
            640                 645                 650

aag tcc gag aca ggg acg cgt gtg ggc gtg gtg cag tac agc cac gag      2077
Lys Ser Glu Thr Gly Thr Arg Val Gly Val Val Gln Tyr Ser His Glu
        655                 660                 665

ggc acc ttt gag gcc atc cag ctg gac gac gaa cat atc gac tcc ctg      2125
Gly Thr Phe Glu Ala Ile Gln Leu Asp Asp Glu His Ile Asp Ser Leu
    670                 675                 680

tcg agc ttc aag gag gct gtc aag aac ctc gag tgg att gcg ggc ggc      2173
Ser Ser Phe Lys Glu Ala Val Lys Asn Leu Glu Trp Ile Ala Gly Gly
685                 690                 695                 700

acc tgg aca ccc tca gcc ctc aag ttt gcc tac gac cgc ctc atc aag      2221
Thr Trp Thr Pro Ser Ala Leu Lys Phe Ala Tyr Asp Arg Leu Ile Lys
                705                 710                 715

gag agc cgg cgc cag aag aca cgt gtg ttt gcg gtg gtc atc acg gac      2269
Glu Ser Arg Arg Gln Lys Thr Arg Val Phe Ala Val Val Ile Thr Asp
            720                 725                 730

ggg cgc cac gac cct cgg gac gat gac ctc aac ttg cgg gcg ctg tgc      2317
Gly Arg His Asp Pro Arg Asp Asp Asp Leu Asn Leu Arg Ala Leu Cys
        735                 740                 745

gac cgc gac gtc aca gtg acg gcc atc ggc atc ggg gac atg ttc cac      2365
Asp Arg Asp Val Thr Val Thr Ala Ile Gly Ile Gly Asp Met Phe His
    750                 755                 760

gag aag cac gag agt gaa aac ctc tac tcc atc gcc tgc gac aag cca      2413
Glu Lys His Glu Ser Glu Asn Leu Tyr Ser Ile Ala Cys Asp Lys Pro
765                 770                 775                 780

cag cag gtg cgc aac atg acg ctg ttc tcc gac ctg gtc gct gag aag      2461
Gln Gln Val Arg Asn Met Thr Leu Phe Ser Asp Leu Val Ala Glu Lys
                785                 790                 795

ttc atc gat gac atg gag gac gtc ctc tgc ccg gac cct cag atc gtg      2509
Phe Ile Asp Asp Met Glu Asp Val Leu Cys Pro Asp Pro Gln Ile Val
            800                 805                 810

tgc cca gac ctt ccc tgc caa aca ggt ttg gac gga gct gtt ttg tgc      2557
Cys Pro Asp Leu Pro Cys Gln Thr Gly Leu Asp Gly Ala Val Leu Cys
        815                 820                 825

tga aaggttttct cggggtccgt ggtgtccccc aaaggtgcca ccgtgcgggt          2610

ctcctagctc cctgccagct tcctgtccct gtgctcactg cccccacgcc tcctgccaag   2670

gccgagccac acacccgctc cacctgcatt tcctctaccg actcgccagc ccaaatgccg   2730

ctcttcactc tggcctcgct gagcggctgc ccgaggagga gctctaggcc gacgcccacc   2790

gcaggcctta cagtcgtctc tggacgctcc cttgcagatg caccgtggcc tggcggcgag   2850

cccccggtca ccttcctccg cacggaagag gggccggacg ccaccttccc caggaccatt   2910
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ccccctgatcc aacagttgct aaacgccacg gagctcacgc aggacccggc cgcctactcc 2970
cagctggtgg ccgtgctggt ctacaccgcc gagcgggcca agttcgccac cggggtagag 3030
cggcaggact ggatggagct gttcattgac acctttaagc tggtgcacag ggacatcgtg 3090
ggggaccccg agaccgcgct ggccctctgc taaagcccgg gcacccgccc agccgggctg 3150
ggccctccct gccacactag cttcccaggg ctgcccccga caggctggct ctcagtggag 3210
gccgagagat ctggaatcgg ggtcagcggg gctacagtcc ttccaggggc tctggggcag 3270
ctcccagcct cttcccatgc tggtggccac cgtgtccctt gctgcggctg catcttccag 3330
tctctcctcc gtcttccagt ggccgctctc tttataagaa ccctggtcat tgaatttaag 3390
gcccacccca agtccagaat gacctcgcaa gacccttaac tcactccc 3438

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<400> 24

Met Leu Gln Gly Thr Cys Ser Val Leu Leu Leu Trp Gly Ile Leu Gly
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Ala Ile Gln Ala Gln Gln Gln Glu Val Ile Ser Pro Asp Thr Thr Glu
20 25 30

Arg Asn Asn Asn Cys Pro Glu Lys Thr Asp Cys Pro Ile His Val Tyr
35 40 45

Phe Val Leu Asp Thr Ser Glu Ser Val Thr Met Gln Ser Pro Thr Asp
50 55 60

Ile Leu Leu Phe His Met Lys Gln Phe Val Pro Gln Phe Ile Ser Gln
65 70 75 80

Leu Gln Asn Glu Phe Tyr Leu Asp Gln Val Ala Leu Ser Trp Arg Tyr
85 90 95

Gly Gly Leu His Phe Ser Asp Gln Val Glu Val Phe Ser Pro Pro Gly
100 105 110

Ser Asp Arg Ala Ser Phe Ile Lys Asn Leu Gln Gly Ile Ser Ser Phe
115 120 125

Arg Arg Gly Thr Phe Thr Asp Cys Ala Leu Ala Asn Met Thr Glu Gln
130 135 140

Ile Arg Gln Asp Arg Ser Lys Gly Thr Val His Phe Ala Val Val Ile
145 150 155 160

Thr Asp Gly His Val Thr Gly Ser Pro Cys Gly Gly Ile Lys Leu Gln
165 170 175

Ala Glu Arg Ala Arg Glu Glu Gly Ile Arg Leu Phe Ala Val Ala Pro
180 185 190

Asn Gln Asn Leu Lys Glu Gln Gly Leu Arg Asp Ile Ala Ser Thr Pro
195 200 205

His Glu Leu Tyr Arg Asn Asp Tyr Ala Thr Met Leu Pro Asp Ser Thr
210 215 220

Glu Ile Asn Gln Asp Thr Ile Asn Arg Ile Ile Lys Val Met Lys His
225 230 235 240

Glu Ala Tyr Gly Glu Cys Tyr Lys Val Ser Cys Leu Glu Ile Pro Gly
245 250 255

Pro Ser Gly Pro Lys Gly Tyr Arg Gly Gln Lys Gly Ala Lys Gly Asn
260 265 270

Met Gly Glu Pro Gly Glu Pro Gly Gln Lys Gly Arg Gln Gly Asp Pro
275 280 285

Gly Ile Glu Gly Pro Ile Gly Phe Pro Gly Pro Lys Gly Val Pro Gly
290 295 300

Phe Lys Gly Glu Lys Gly Glu Phe Gly Ala Asp Gly Arg Lys Gly Ala
305 310 315 320

Pro Gly Leu Ala Gly Lys Asn Gly Thr Asp Gly Gln Lys Gly Lys Leu
325 330 335

Gly Arg Ile Gly Pro Pro Gly Cys Lys Gly Asp Pro Gly Asn Arg Gly
340 345 350

Pro Asp Gly Tyr Pro Gly Glu Ala Gly Ser Pro Gly Glu Arg Gly Asp
355 360 365

Gln Gly Gly Lys Gly Asp Pro Gly Arg Pro Gly Arg Arg Gly Pro Pro
370 375 380

Gly Glu Ile Gly Ala Lys Gly Ser Lys Gly Tyr Gln Gly Asn Asn Gly
385 390 395 400

Ala Pro Gly Ser Pro Gly Val Lys Gly Ala Lys Gly Gly Pro Gly Pro
405 410 415

Arg Gly Pro Lys Gly Glu Pro Gly Arg Arg Gly Asp Pro Gly Thr Lys
420 425 430

Gly Ser Pro Gly Ser Asp Gly Pro Lys Gly Glu Lys Gly Asp Pro Gly
435 440 445

Pro Glu Gly Pro Arg Gly Leu Ala Gly Glu Val Gly Asn Lys Gly Ala
450 455 460

Lys Gly Asp Arg Gly Leu Pro Gly Pro Arg Gly Pro Gln Gly Ala Leu
465 470 475 480

Gly Glu Pro Gly Lys Gln Gly Ser Arg Gly Asp Pro Gly Asp Ala Gly
485 490 495

Pro Arg Gly Asp Ser Gly Gln Pro Gly Pro Lys Gly Asp Pro Gly Arg
500 505 510

Pro Gly Phe Ser Tyr Pro Gly Pro Arg Gly Ala Pro Gly Glu Lys Gly
515 520 525

Glu Pro Gly Pro Arg Gly Pro Glu Gly Gly Arg Gly Asp Phe Gly Leu
530 535 540

Lys Gly Glu Pro Gly Arg Lys Gly Glu Lys Gly Glu Pro Ala Asp Pro
545 550 555 560

Gly Pro Pro Gly Glu Pro Gly Pro Arg Gly Pro Arg Gly Val Pro Gly
565 570 575

Pro Glu Gly Glu Pro Gly Pro Pro Gly Asp Pro Gly Leu Thr Glu Cys
580 585 590

Asp Val Met Thr Tyr Val Arg Glu Thr Cys Gly Cys Cys Asp Cys Glu
595 600 605

Lys Arg Cys Gly Ala Leu Asp Val Val Phe Val Ile Asp Ser Ser Glu
610 615 620

Ser Ile Gly Tyr Thr Asn Phe Thr Leu Glu Lys Asn Phe Val Ile Asn
625 630 635 640

Val Val Asn Arg Leu Gly Ala Ile Ala Lys Asp Pro Lys Ser Glu Thr
645 650 655

Gly Thr Arg Val Gly Val Val Gln Tyr Ser His Glu Gly Thr Phe Glu
660 665 670

Ala Ile Gln Leu Asp Asp Glu His Ile Asp Ser Leu Ser Ser Phe Lys
675 680 685

Glu Ala Val Lys Asn Leu Glu Trp Ile Ala Gly Gly Thr Trp Thr Pro
690 695 700

Ser Ala Leu Lys Phe Ala Tyr Asp Arg Leu Ile Lys Glu Ser Arg Arg
705 710 715 720

Gln Lys Thr Arg Val Phe Ala Val Val Ile Thr Asp Gly Arg His Asp
725 730 735

Pro Arg Asp Asp Asp Leu Asn Leu Arg Ala Leu Cys Asp Arg Asp Val
740 745 750

Thr Val Thr Ala Ile Gly Ile Gly Asp Met Phe His Glu Lys His Glu
755 760 765

Ser Glu Asn Leu Tyr Ser Ile Ala Cys Asp Lys Pro Gln Gln Val Arg
770 775 780

Asn Met Thr Leu Phe Ser Asp Leu Val Ala Glu Lys Phe Ile Asp Asp
785 790 795 800

Met Glu Asp Val Leu Cys Pro Asp Pro Gln Ile Val Cys Pro Asp Leu
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Pro Cys Gln Thr Gly Leu Asp Gly Ala Val Leu Cys
820 825

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<400> 25

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cggggctggt cgcctgcagg g atg ggg gac gag cgg ccc cac tac tac ggg       111
                        Met Gly Asp Glu Arg Pro His Tyr Tyr Gly
                        1               5                  10

aaa cac gga acg cca cag aag tat gat ccc act ttc aaa gga ccc att       159
Lys His Gly Thr Pro Gln Lys Tyr Asp Pro Thr Phe Lys Gly Pro Ile
                    15                  20                  25

tac aat agg ggc tgc acg gat atc ata tgc tgt gtg ttc ctg ctc ctg       207
Tyr Asn Arg Gly Cys Thr Asp Ile Ile Cys Cys Val Phe Leu Leu Leu
                30                  35                  40

gcc att gtg ggc tac gtg gct gta ggc atc ata gcc tgg act cat gga       255
Ala Ile Val Gly Tyr Val Ala Val Gly Ile Ile Ala Trp Thr His Gly
            45                  50                  55

gac cct cga aag gtg atc tac ccc act gat agc cgg ggc gag ttc tgc       303
Asp Pro Arg Lys Val Ile Tyr Pro Thr Asp Ser Arg Gly Glu Phe Cys
        60                  65                  70

ggg cag aag ggc aca aaa aac gag aac aaa ccc tat ctg ttt tat ttc       351
Gly Gln Lys Gly Thr Lys Asn Glu Asn Lys Pro Tyr Leu Phe Tyr Phe
75                  80                  85                  90

aac att gtg aaa tgt gcc agc ccc ctg gtt ctg ctg gaa ttc caa tgt       399
Asn Ile Val Lys Cys Ala Ser Pro Leu Val Leu Leu Glu Phe Gln Cys
                95                  100                 105

ccc act ccc cag atc tgc gtg gaa aaa tgc ccc gac cgc tac ctc acg       447
Pro Thr Pro Gln Ile Cys Val Glu Lys Cys Pro Asp Arg Tyr Leu Thr
            110                 115                 120

tac ctg aat gct cgc agc tcc cgg gac ttt gag tac tat aag cag ttc       495
Tyr Leu Asn Ala Arg Ser Ser Arg Asp Phe Glu Tyr Tyr Lys Gln Phe
        125                 130                 135

tgt gtt cct ggc ttc aag aac aat aaa gga gtg gct gag gtg ctt cga       543
Cys Val Pro Gly Phe Lys Asn Asn Lys Gly Val Ala Glu Val Leu Arg
    140                 145                 150

gat ggt gac tgc cct gct gtc ctc atc ccc agc aaa ccc ttg gcc cgg       591
Asp Gly Asp Cys Pro Ala Val Leu Ile Pro Ser Lys Pro Leu Ala Arg
155                 160                 165                 170

aga tgc ttc ccc gct atc cac gcc tac aag ggt gtc ctg atg gtg ggc       639
Arg Cys Phe Pro Ala Ile His Ala Tyr Lys Gly Val Leu Met Val Gly
                175                 180                 185

aat gag acg acc tat gag gat ggg cat ggc tcc cgg aaa aac atc aca       687
Asn Glu Thr Thr Tyr Glu Asp Gly His Gly Ser Arg Lys Asn Ile Thr
            190                 195                 200

gac ctg gtg gag ggc gcc aag aaa gcc aat gga gtc cta gag gcg cgg       735
Asp Leu Val Glu Gly Ala Lys Lys Ala Asn Gly Val Leu Glu Ala Arg
        205                 210                 215

caa ctc gcc atg cgc ata ttt gaa gat tac acc gtc tct tgg tac tgg       783
Gln Leu Ala Met Arg Ile Phe Glu Asp Tyr Thr Val Ser Trp Tyr Trp
    220                 225                 230

att atc ata ggc ctg gtc att gcc atg gcg atg agc ctc ctg ttc atc       831
Ile Ile Ile Gly Leu Val Ile Ala Met Ala Met Ser Leu Leu Phe Ile
235                 240                 245                 250

atc ctg ctt cgc ttc ctg gct ggt att atg gtc tgg gtg atg atc atc       879
Ile Leu Leu Arg Phe Leu Ala Gly Ile Met Val Trp Val Met Ile Ile
                255                 260                 265

atg gtg att ctg gtg ctg ggc tac gga ata ttt cac tgc tac atg gag       927
Met Val Ile Leu Val Leu Gly Tyr Gly Ile Phe His Cys Tyr Met Glu
            270                 275                 280

tac tcc cga ctg cgt ggt gag gcc ggc tct gat gtc tct ttg gtg gac       975
Tyr Ser Arg Leu Arg Gly Glu Ala Gly Ser Asp Val Ser Leu Val Asp
        285                 290                 295
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ctc ggc ttt cag acg gat ttc cgg gtg tac ctg cac tta cgg cag acc      1023
Leu Gly Phe Gln Thr Asp Phe Arg Val Tyr Leu His Leu Arg Gln Thr
    300                 305                 310

tgg ttg gcc ttt atg atc att ctg agt atc ctt gaa gtc att atc atc      1071
Trp Leu Ala Phe Met Ile Ile Leu Ser Ile Leu Glu Val Ile Ile Ile
315                 320                 325                 330

ttg ctg ctc atc ttt ctc cgg aag aga att ctc atc gcg att gca ctc      1119
Leu Leu Leu Ile Phe Leu Arg Lys Arg Ile Leu Ile Ala Ile Ala Leu
                335                 340                 345

atc aaa gaa gcc agc agg gct gtg gga tac gtc atg tgc tcc ttg ctc      1167
Ile Lys Glu Ala Ser Arg Ala Val Gly Tyr Val Met Cys Ser Leu Leu
            350                 355                 360

tac cca ctg gtc acc ttc ttc ttg ctg tgc ctc tgc atc gcc tac tgg      1215
Tyr Pro Leu Val Thr Phe Phe Leu Leu Cys Leu Cys Ile Ala Tyr Trp
        365                 370                 375

gcc agc act gct gtc ttc ctg tcc act tcc aac gaa gcg gtc tat aag      1263
Ala Ser Thr Ala Val Phe Leu Ser Thr Ser Asn Glu Ala Val Tyr Lys
    380                 385                 390

atc ttt gat gac agc ccc tgc cca ttt act gcg aaa acc tgc aac cca      1311
Ile Phe Asp Asp Ser Pro Cys Pro Phe Thr Ala Lys Thr Cys Asn Pro
395                 400                 405                 410

gag acc ttc ccc tcc tcc aat gag tcc cgc caa tgc ccc aat gcc cgt      1359
Glu Thr Phe Pro Ser Ser Asn Glu Ser Arg Gln Cys Pro Asn Ala Arg
                415                 420                 425

tgc cag ttc gcc ttc tac ggt ggt gag tcg ggc tac cac cgg gcc ctg      1407
Cys Gln Phe Ala Phe Tyr Gly Gly Glu Ser Gly Tyr His Arg Ala Leu
            430                 435                 440

ctg ggc ctg cag atc ttc aat gcc ttc atg ttc ttc tgg ttg gcc aac      1455
Leu Gly Leu Gln Ile Phe Asn Ala Phe Met Phe Phe Trp Leu Ala Asn
        445                 450                 455

ttc gtg ctg gcg ctg ggc cag gtc acg ctg gcc ggg gcc ttt gcc tcc      1503
Phe Val Leu Ala Leu Gly Gln Val Thr Leu Ala Gly Ala Phe Ala Ser
    460                 465                 470

tac tac tgg gcc ctg cgc aag ccg gac gac ctg ccg gcc ttc ccg ctc      1551
Tyr Tyr Trp Ala Leu Arg Lys Pro Asp Asp Leu Pro Ala Phe Pro Leu
475                 480                 485                 490

ttc tct gcc ttt ggc cgg gcg ctc agg tac cac aca ggc tcc ctg gcc      1599
Phe Ser Ala Phe Gly Arg Ala Leu Arg Tyr His Thr Gly Ser Leu Ala
                495                 500                 505

ttt ggc gcg ctc atc ctg gcc att gtg cag atc atc cgt gtg ata ctc      1647
Phe Gly Ala Leu Ile Leu Ala Ile Val Gln Ile Ile Arg Val Ile Leu
            510                 515                 520

gag tac ctg gat cag cgg ctg aaa gct gca gag aac aag ttt gcc aag      1695
Glu Tyr Leu Asp Gln Arg Leu Lys Ala Ala Glu Asn Lys Phe Ala Lys
        525                 530                 535

tgc ctc atg acc tgt ctc aaa tgc tgc ttc tgg tgc ctg gag aag ttc      1743
Cys Leu Met Thr Cys Leu Lys Cys Cys Phe Trp Cys Leu Glu Lys Phe
    540                 545                 550

atc aaa ttc ctt aat agg aat gcc tac atc atg att gcc atc tac ggc      1791
Ile Lys Phe Leu Asn Arg Asn Ala Tyr Ile Met Ile Ala Ile Tyr Gly
555                 560                 565                 570

acc aat ttc tgc acc tcg gcc agg aat gcc ttc ttc ctg ctc atg aga      1839
Thr Asn Phe Cys Thr Ser Ala Arg Asn Ala Phe Phe Leu Leu Met Arg
                575                 580                 585

aac atc atc aga gtg gct gtc ctg gat aaa gtt act gac ttc ctc ttc      1887
Asn Ile Ile Arg Val Ala Val Leu Asp Lys Val Thr Asp Phe Leu Phe
            590                 595                 600

ctg ttg ggc aaa ctt ctg atc gtt ggt agt gtg ggg atc ctg gct ttc      1935
Leu Leu Gly Lys Leu Leu Ile Val Gly Ser Val Gly Ile Leu Ala Phe
        605                 610                 615
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ttc ttc ttc acc cac cgt atc agg atc gtg cag gat aca gca cca ccc 1983
Phe Phe Phe Thr His Arg Ile Arg Ile Val Gln Asp Thr Ala Pro Pro
620 625 630

ctc aat tat tac tgg gtt cct ata ctg acg gtg atc gtt ggc tcc tac 2031
Leu Asn Tyr Tyr Trp Val Pro Ile Leu Thr Val Ile Val Gly Ser Tyr
635 640 645 650

ttg att gca cac ggt ttc ttc agc gtc tat ggc atg tgt gtg gac acg 2079
Leu Ile Ala His Gly Phe Phe Ser Val Tyr Gly Met Cys Val Asp Thr
655 660 665

ctg ttc ctc tgc ttc ttg gag gac ctg gag agg aat gac ggc tcg gcc 2127
Leu Phe Leu Cys Phe Leu Glu Asp Leu Glu Arg Asn Asp Gly Ser Ala
670 675 680

gag agg cct tac ttc atg tct tcc acc ctc aag aaa ccc ttg aac aag 2175
Glu Arg Pro Tyr Phe Met Ser Ser Thr Leu Lys Lys Pro Leu Asn Lys
685 690 695

acc aac aag aag gca gcg gag tcc tga aggccccgtg ctccccacct 2222
Thr Asn Lys Lys Ala Ala Glu Ser
700 705

ctcaaggagt ctcatgccgc agggtgctca gtagctgggt ctgttccccc agccccttgg 2282

gctcacctga agtcctatca ctgccgctct gcccctcccc atgagccaga tcccaccagt 2342

ttctggacgt ggagagtctg gggcatctcc ttcttatgcc aaggggcgct tggagttttc 2402

atggctgccc ctccagactg cgagaaacaa gtaaaaaccc attggggcct cttgatgtct 2462

gggatggcac gtggcccgac ctccacaagc tccctcatgc ttcctgtccc ccgcttacac 2522

gacaacgggc cagaccacgg gaaggacggt gtttgtgtct gagggagctg ctggccacag 2582

tgaacaccca cgtttattcc tgcctgctcc ggccaggact gaacccccttc tccacacctg 2642

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cccctggccc caggggaaag agggggggt ctcccgtttc ctgtgcctgc accagccctg 3302

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attgtacagg taaaaaaaaa aaaaaaa 3389

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Lys Tyr Asp Pro Thr Phe Lys Gly Pro Ile Tyr Asn Arg Gly Cys Thr
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Asp Ile Ile Cys Cys Val Phe Leu Leu Leu Ala Ile Val Gly Tyr Val
35 40 45

Ala Val Gly Ile Ile Ala Trp Thr His Gly Asp Pro Arg Lys Val Ile
50 55 60

Tyr Pro Thr Asp Ser Arg Gly Glu Phe Cys Gly Gln Lys Gly Thr Lys
65 70 75 80

Asn Glu Asn Lys Pro Tyr Leu Phe Tyr Phe Asn Ile Val Lys Cys Ala
85 90 95

Ser Pro Leu Val Leu Leu Glu Phe Gln Cys Pro Thr Pro Gln Ile Cys
100 105 110

Val Glu Lys Cys Pro Asp Arg Tyr Leu Thr Tyr Leu Asn Ala Arg Ser
115 120 125

Ser Arg Asp Phe Glu Tyr Tyr Lys Gln Phe Cys Val Pro Gly Phe Lys
130 135 140

Asn Asn Lys Gly Val Ala Glu Val Leu Arg Asp Gly Asp Cys Pro Ala
145 150 155 160

Val Leu Ile Pro Ser Lys Pro Leu Ala Arg Arg Cys Phe Pro Ala Ile
165 170 175

His Ala Tyr Lys Gly Val Leu Met Val Gly Asn Glu Thr Thr Tyr Glu
180 185 190

Asp Gly His Gly Ser Arg Lys Asn Ile Thr Asp Leu Val Glu Gly Ala
195 200 205

Lys Lys Ala Asn Gly Val Leu Glu Ala Arg Gln Leu Ala Met Arg Ile
210 215 220

Phe Glu Asp Tyr Thr Val Ser Trp Tyr Trp Ile Ile Ile Gly Leu Val
225 230 235 240

Ile Ala Met Ala Met Ser Leu Leu Phe Ile Ile Leu Leu Arg Phe Leu
245 250 255

Ala Gly Ile Met Val Trp Val Met Ile Ile Met Val Ile Leu Val Leu
260 265 270

Gly Tyr Gly Ile Phe His Cys Tyr Met Glu Tyr Ser Arg Leu Arg Gly
275 280 285

Glu Ala Gly Ser Asp Val Ser Leu Val Asp Leu Gly Phe Gln Thr Asp
290 295 300

Phe Arg Val Tyr Leu His Leu Arg Gln Thr Trp Leu Ala Phe Met Ile
305 310 315 320

Ile Leu Ser Ile Leu Glu Val Ile Ile Ile Leu Leu Leu Ile Phe Leu
325 330 335

Arg Lys Arg Ile Leu Ile Ala Ile Ala Leu Ile Lys Glu Ala Ser Arg
340 345 350

Ala Val Gly Tyr Val Met Cys Ser Leu Leu Tyr Pro Leu Val Thr Phe
355 360 365

Phe Leu Leu Cys Leu Cys Ile Ala Tyr Trp Ala Ser Thr Ala Val Phe
370 375 380

Leu Ser Thr Ser Asn Glu Ala Val Tyr Lys Ile Phe Asp Asp Ser Pro
385 390 395 400

Cys Pro Phe Thr Ala Lys Thr Cys Asn Pro Glu Thr Phe Pro Ser Ser
405 410 415

Asn Glu Ser Arg Gln Cys Pro Asn Ala Arg Cys Gln Phe Ala Phe Tyr
420 425 430

Gly Gly Glu Ser Gly Tyr His Arg Ala Leu Leu Gly Leu Gln Ile Phe
435 440 445

Asn Ala Phe Met Phe Phe Trp Leu Ala Asn Phe Val Leu Ala Leu Gly
450 455 460

Gln Val Thr Leu Ala Gly Ala Phe Ala Ser Tyr Tyr Trp Ala Leu Arg
465 470 475 480

Lys Pro Asp Asp Leu Pro Ala Phe Pro Leu Phe Ser Ala Phe Gly Arg
485 490 495

Ala Leu Arg Tyr His Thr Gly Ser Leu Ala Phe Gly Ala Leu Ile Leu
500 505 510

Ala Ile Val Gln Ile Ile Arg Val Ile Leu Glu Tyr Leu Asp Gln Arg
515 520 525

Leu Lys Ala Ala Glu Asn Lys Phe Ala Lys Cys Leu Met Thr Cys Leu
530 535 540

Lys Cys Cys Phe Trp Cys Leu Glu Lys Phe Ile Lys Phe Leu Asn Arg
545 550 555 560

Asn Ala Tyr Ile Met Ile Ala Ile Tyr Gly Thr Asn Phe Cys Thr Ser
565 570 575

Ala Arg Asn Ala Phe Phe Leu Leu Met Arg Asn Ile Ile Arg Val Ala
580 585 590

Val Leu Asp Lys Val Thr Asp Phe Leu Phe Leu Leu Gly Lys Leu Leu
595 600 605

Ile Val Gly Ser Val Gly Ile Leu Ala Phe Phe Phe Phe Thr His Arg
610 615 620

Ile Arg Ile Val Gln Asp Thr Ala Pro Pro Leu Asn Tyr Tyr Trp Val
625 630 635 640

Pro Ile Leu Thr Val Ile Val Gly Ser Tyr Leu Ile Ala His Gly Phe
645 650 655

Phe Ser Val Tyr Gly Met Cys Val Asp Thr Leu Phe Leu Cys Phe Leu
660 665 670

Glu Asp Leu Glu Arg Asn Asp Gly Ser Ala Glu Arg Pro Tyr Phe Met
675 680 685

Ser Ser Thr Leu Lys Lys Pro Leu Asn Lys Thr Asn Lys Lys Ala Ala
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Glu Ser
705

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Met Arg Gly Val Trp Pro Pro Pro Val Ser Ala Leu Leu Ser Ala Leu
1               5                  10                  15

ggg atg tcg acg tac aag cgg gcc acg ctg gac gag gag gac ctg gtg        96
Gly Met Ser Thr Tyr Lys Arg Ala Thr Leu Asp Glu Glu Asp Leu Val
            20                  25                  30

gac tcg ctc tcc gag ggc gac gca tac ccc aac ggc ctg cag gtg aac       144
Asp Ser Leu Ser Glu Gly Asp Ala Tyr Pro Asn Gly Leu Gln Val Asn
        35                  40                  45

ttc cac agc ccc cgg agt ggc cag agg tgc tgg gct gca cgg acc cag       192
Phe His Ser Pro Arg Ser Gly Gln Arg Cys Trp Ala Ala Arg Thr Gln
    50                  55                  60

gtg gag aag cgg ctg gtg gtg ttg gtg gta ctt ctg gcg gca gga ctg       240
Val Glu Lys Arg Leu Val Val Leu Val Val Leu Leu Ala Ala Gly Leu
65                  70                  75                  80

gtg gcc tgc ttg gca gca ctg ggc atc cag tac cag aca aga tcc ccc       288
Val Ala Cys Leu Ala Ala Leu Gly Ile Gln Tyr Gln Thr Arg Ser Pro
                85                  90                  95

tct gtg tgc ctg agc gaa gct tgt gtc tca gtg acc agc tcc atc ttg       336
Ser Val Cys Leu Ser Glu Ala Cys Val Ser Val Thr Ser Ser Ile Leu
            100                 105                 110

agc tcc atg gac ccc aca gtg gac ccc tgc cat gac ttc ttc agc tac       384
Ser Ser Met Asp Pro Thr Val Asp Pro Cys His Asp Phe Phe Ser Tyr
        115                 120                 125

gcc tgt ggg ggc tgg atc aag gcc aac cca gtc cct gat ggc cac tca       432
Ala Cys Gly Gly Trp Ile Lys Ala Asn Pro Val Pro Asp Gly His Ser
    130                 135                 140

cgc tgg ggg acc ttc agc aac ctc tgg gaa cac aac caa gca atc atc       480
Arg Trp Gly Thr Phe Ser Asn Leu Trp Glu His Asn Gln Ala Ile Ile
145                 150                 155                 160

aag cac ctc ctc gaa aac tcc acg gcc agc gtg agc gag gca gag aga       528
Lys His Leu Leu Glu Asn Ser Thr Ala Ser Val Ser Glu Ala Glu Arg
                165                 170                 175

aag gcg caa gta tac tac cgt gcg tgc atg aac gag acc agg atc gag       576
Lys Ala Gln Val Tyr Tyr Arg Ala Cys Met Asn Glu Thr Arg Ile Glu
            180                 185                 190

gag ctc agg gcc aaa cct cta atg gag ttg att gag agg ctc ggg ggc       624
Glu Leu Arg Ala Lys Pro Leu Met Glu Leu Ile Glu Arg Leu Gly Gly
        195                 200                 205

tgg aac atc aca ggt ccc tgg gcc aag gac aac ttc cag gac acc ctg       672
Trp Asn Ile Thr Gly Pro Trp Ala Lys Asp Asn Phe Gln Asp Thr Leu
    210                 215                 220

cag gtg gtc acc gcc cac tac cgc acc tca ccc ttc ttc tct gtc tat       720
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Gln Val Val Thr Ala His Tyr Arg Thr Ser Pro Phe Phe Ser Val Tyr
225                 230                 235                 240

gtc agt gcc gat tcc aag aac tcc aac agc aac gtg atc cag gtg gac      768
Val Ser Ala Asp Ser Lys Asn Ser Asn Ser Asn Val Ile Gln Val Asp
                245                 250                 255

cag tct ggc ctg ggc ttg ccc tcg aga gac tat tac ctg aac aaa act      816
Gln Ser Gly Leu Gly Leu Pro Ser Arg Asp Tyr Tyr Leu Asn Lys Thr
            260                 265                 270

gaa aac gag aag gtg ctg acc gga tat ctg aac tac atg gtc cag ctg      864
Glu Asn Glu Lys Val Leu Thr Gly Tyr Leu Asn Tyr Met Val Gln Leu
        275                 280                 285

ggg aag ctg ctg ggc ggc ggg gac gag gag gcc atc cgg ccc cag atg      912
Gly Lys Leu Leu Gly Gly Gly Asp Glu Glu Ala Ile Arg Pro Gln Met
    290                 295                 300

cag cag atc ttg gac ttt gag acg gca ctg gcc aac atc acc atc cca      960
Gln Gln Ile Leu Asp Phe Glu Thr Ala Leu Ala Asn Ile Thr Ile Pro
305                 310                 315                 320

cag gag aag cgc cgt gat gag gag ctc atc tac cac aaa gtg acg gca     1008
Gln Glu Lys Arg Arg Asp Glu Glu Leu Ile Tyr His Lys Val Thr Ala
                325                 330                 335

gcc gag ctg cag acc ttg gca ccc gcc atc aac tgg ttg cct ttt ctc     1056
Ala Glu Leu Gln Thr Leu Ala Pro Ala Ile Asn Trp Leu Pro Phe Leu
            340                 345                 350

aac acc atc ttc tac ccc gtg gag atc aat gaa tcc gag cct att gtg     1104
Asn Thr Ile Phe Tyr Pro Val Glu Ile Asn Glu Ser Glu Pro Ile Val
        355                 360                 365

gtc tat gac aag gaa tac ctt gag cag atc tcc act ctc atc aac acc     1152
Val Tyr Asp Lys Glu Tyr Leu Glu Gln Ile Ser Thr Leu Ile Asn Thr
    370                 375                 380

acc gac aga tgc ctg ctc aac aac tac atg atc tgg aac ctg gtg cgg     1200
Thr Asp Arg Cys Leu Leu Asn Asn Tyr Met Ile Trp Asn Leu Val Arg
385                 390                 395                 400

aaa aca agc tcc ttc ctt gac cag cgc ttt cag gac gcc gat gag aag     1248
Lys Thr Ser Ser Phe Leu Asp Gln Arg Phe Gln Asp Ala Asp Glu Lys
                405                 410                 415

ttc atg gaa gtc atg tac ggg acc aag aag acc tgt ctt cct cgc tgg     1296
Phe Met Glu Val Met Tyr Gly Thr Lys Lys Thr Cys Leu Pro Arg Trp
            420                 425                 430

aag ttt tgc gtg agt gac aca gaa aac aac ctg ggc ttt gcg ttg ggc     1344
Lys Phe Cys Val Ser Asp Thr Glu Asn Asn Leu Gly Phe Ala Leu Gly
        435                 440                 445

ccc atg ttt gtc aaa gca acc ttc gcc gag gac agc aag agc ata gcc     1392
Pro Met Phe Val Lys Ala Thr Phe Ala Glu Asp Ser Lys Ser Ile Ala
    450                 455                 460

acc gag atc atc ctg gag att aag aag gca ttt gag gaa agc ctg agc     1440
Thr Glu Ile Ile Leu Glu Ile Lys Lys Ala Phe Glu Glu Ser Leu Ser
465                 470                 475                 480

acc ctg aag tgg atg gat gag gaa acc cga aaa tca gcc aag gaa aag     1488
Thr Leu Lys Trp Met Asp Glu Glu Thr Arg Lys Ser Ala Lys Glu Lys
                485                 490                 495

gcc gat gcc atc tac aac atg ata gga tac ccc aac ttc atc atg gat     1536
Ala Asp Ala Ile Tyr Asn Met Ile Gly Tyr Pro Asn Phe Ile Met Asp
            500                 505                 510

ccc aag gag ctg gac aaa gtg ttt aat gac tac act gca gtt cca gac     1584
Pro Lys Glu Leu Asp Lys Val Phe Asn Asp Tyr Thr Ala Val Pro Asp
        515                 520                 525

ctc tac ttt gaa aat gcc atg cgg ttt ttc aac ttc tca tgg agg gtc     1632
Leu Tyr Phe Glu Asn Ala Met Arg Phe Phe Asn Phe Ser Trp Arg Val
    530                 535                 540

act gcc gat cag ctc agg aaa gcc ccc aac aga gat cag tgg agc atg     1680
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Thr Ala Asp Gln Leu Arg Lys Ala Pro Asn Arg Asp Gln Trp Ser Met
545                 550                 555                 560

acc ccg ccc atg gtg aac gcc tac tac tcg ccc acc aag aat gag att      1728
Thr Pro Pro Met Val Asn Ala Tyr Tyr Ser Pro Thr Lys Asn Glu Ile
                565                 570                 575

gtg ttt ccg gcc ggg atc ctg cag gca cca ttc tac aca cgc tcc tca      1776
Val Phe Pro Ala Gly Ile Leu Gln Ala Pro Phe Tyr Thr Arg Ser Ser
            580                 585                 590

ccc aag gcc tta aac ttt ggt ggc ata ggt gtc gtc gtg ggc cat gag      1824
Pro Lys Ala Leu Asn Phe Gly Gly Ile Gly Val Val Val Gly His Glu
        595                 600                 605

ctg act cat gct ttt gat gat caa gga cgg gag tat gac aag gac ggg      1872
Leu Thr His Ala Phe Asp Asp Gln Gly Arg Glu Tyr Asp Lys Asp Gly
    610                 615                 620

aac ctc cgg cca tgg tgg aag aac tca tcc gtg gag gcc ttc aag cgt      1920
Asn Leu Arg Pro Trp Trp Lys Asn Ser Ser Val Glu Ala Phe Lys Arg
625                 630                 635                 640

cag acc gag tgc atg gta gag cag tac agc aac tac agc gtg aac ggg      1968
Gln Thr Glu Cys Met Val Glu Gln Tyr Ser Asn Tyr Ser Val Asn Gly
                645                 650                 655

gag ccg gtg aac ggg cgg cac acc ctg ggg gag aac atc gcc gac aac      2016
Glu Pro Val Asn Gly Arg His Thr Leu Gly Glu Asn Ile Ala Asp Asn
            660                 665                 670

ggg ggt ctc aag gcg gcc tat cgg gct tac cag aac tgg gtg aag aag      2064
Gly Gly Leu Lys Ala Ala Tyr Arg Ala Tyr Gln Asn Trp Val Lys Lys
        675                 680                 685

aac ggg gct gag cac tcg ctc ccc acc ctg ggc ctc acc aat aac cag      2112
Asn Gly Ala Glu His Ser Leu Pro Thr Leu Gly Leu Thr Asn Asn Gln
    690                 695                 700

ctc ttc ttc ctg ggc ttt gca cag gtc tgg tgc tcc gtc cgc aca cct      2160
Leu Phe Phe Leu Gly Phe Ala Gln Val Trp Cys Ser Val Arg Thr Pro
705                 710                 715                 720

gag agc tcc cac gaa ggc ctc atc acc gat ccc cac agc ccc tct cgc      2208
Glu Ser Ser His Glu Gly Leu Ile Thr Asp Pro His Ser Pro Ser Arg
                725                 730                 735

ttc cgg gtc atc ggc tcc ctc tcc aat tcc aag gag ttc tca gaa cac      2256
Phe Arg Val Ile Gly Ser Leu Ser Asn Ser Lys Glu Phe Ser Glu His
            740                 745                 750

ttc cgc tgc cca cct ggc tca ccc atg aac ccg cct cac aag tgc gaa      2304
Phe Arg Cys Pro Pro Gly Ser Pro Met Asn Pro Pro His Lys Cys Glu
        755                 760                 765

gtc tgg taa ggacgaagcg gagagagcca agacggagga ggggaagggg              2353
Val Trp
    770

ctgaggacga gacccccatc cagcctccag ggcattgctc agcccgcttg gccacc        2409


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            20                  25                  30

Asp Ser Leu Ser Glu Gly Asp Ala Tyr Pro Asn Gly Leu Gln Val Asn
        35                  40                  45
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Phe His Ser Pro Arg Ser Gly Gln Arg Cys Trp Ala Ala Arg Thr Gln
50 55 60

Val Glu Lys Arg Leu Val Val Leu Val Val Leu Leu Ala Ala Gly Leu
65 70 75 80

Val Ala Cys Leu Ala Ala Leu Gly Ile Gln Tyr Gln Thr Arg Ser Pro
85 90 95

Ser Val Cys Leu Ser Glu Ala Cys Val Ser Val Thr Ser Ser Ile Leu
100 105 110

Ser Ser Met Asp Pro Thr Val Asp Pro Cys His Asp Phe Phe Ser Tyr
115 120 125

Ala Cys Gly Gly Trp Ile Lys Ala Asn Pro Val Pro Asp Gly His Ser
130 135 140

Arg Trp Gly Thr Phe Ser Asn Leu Trp Glu His Asn Gln Ala Ile Ile
145 150 155 160

Lys His Leu Leu Glu Asn Ser Thr Ala Ser Val Ser Glu Ala Glu Arg
165 170 175

Lys Ala Gln Val Tyr Tyr Arg Ala Cys Met Asn Glu Thr Arg Ile Glu
180 185 190

Glu Leu Arg Ala Lys Pro Leu Met Glu Leu Ile Glu Arg Leu Gly Gly
195 200 205

Trp Asn Ile Thr Gly Pro Trp Ala Lys Asp Asn Phe Gln Asp Thr Leu
210 215 220

Gln Val Val Thr Ala His Tyr Arg Thr Ser Pro Phe Phe Ser Val Tyr
225 230 235 240

Val Ser Ala Asp Ser Lys Asn Ser Asn Ser Asn Val Ile Gln Val Asp
245 250 255

Gln Ser Gly Leu Gly Leu Pro Ser Arg Asp Tyr Tyr Leu Asn Lys Thr
260 265 270

Glu Asn Glu Lys Val Leu Thr Gly Tyr Leu Asn Tyr Met Val Gln Leu
275 280 285

Gly Lys Leu Leu Gly Gly Gly Asp Glu Glu Ala Ile Arg Pro Gln Met
290 295 300

Gln Gln Ile Leu Asp Phe Glu Thr Ala Leu Ala Asn Ile Thr Ile Pro
305 310 315 320

Gln Glu Lys Arg Arg Asp Glu Glu Leu Ile Tyr His Lys Val Thr Ala
325 330 335

Ala Glu Leu Gln Thr Leu Ala Pro Ala Ile Asn Trp Leu Pro Phe Leu
340 345 350

Asn Thr Ile Phe Tyr Pro Val Glu Ile Asn Glu Ser Glu Pro Ile Val
355 360 365

Val Tyr Asp Lys Glu Tyr Leu Glu Gln Ile Ser Thr Leu Ile Asn Thr
370 375 380

Thr Asp Arg Cys Leu Leu Asn Asn Tyr Met Ile Trp Asn Leu Val Arg
385 390 395 400

Lys Thr Ser Ser Phe Leu Asp Gln Arg Phe Gln Asp Ala Asp Glu Lys
405 410 415

Phe Met Glu Val Met Tyr Gly Thr Lys Lys Thr Cys Leu Pro Arg Trp
420 425 430

Lys Phe Cys Val Ser Asp Thr Glu Asn Asn Leu Gly Phe Ala Leu Gly
435 440 445

Pro Met Phe Val Lys Ala Thr Phe Ala Glu Asp Ser Lys Ser Ile Ala
450 455 460

Thr Glu Ile Ile Leu Glu Ile Lys Lys Ala Phe Glu Glu Ser Leu Ser
465 470 475 480

Thr Leu Lys Trp Met Asp Glu Glu Thr Arg Lys Ser Ala Lys Glu Lys
485 490 495

Ala Asp Ala Ile Tyr Asn Met Ile Gly Tyr Pro Asn Phe Ile Met Asp
500 505 510

Pro Lys Glu Leu Asp Lys Val Phe Asn Asp Tyr Thr Ala Val Pro Asp
515 520 525

Leu Tyr Phe Glu Asn Ala Met Arg Phe Phe Asn Phe Ser Trp Arg Val
530 535 540

Thr Ala Asp Gln Leu Arg Lys Ala Pro Asn Arg Asp Gln Trp Ser Met
545 550 555 560

Thr Pro Pro Met Val Asn Ala Tyr Tyr Ser Pro Thr Lys Asn Glu Ile
565 570 575

Val Phe Pro Ala Gly Ile Leu Gln Ala Pro Phe Tyr Thr Arg Ser Ser
580 585 590

Pro Lys Ala Leu Asn Phe Gly Gly Ile Gly Val Val Val Gly His Glu
595 600 605

Leu Thr His Ala Phe Asp Asp Gln Gly Arg Glu Tyr Asp Lys Asp Gly
610 615 620

Asn Leu Arg Pro Trp Trp Lys Asn Ser Ser Val Glu Ala Phe Lys Arg
625 630 635 640

Gln Thr Glu Cys Met Val Glu Gln Tyr Ser Asn Tyr Ser Val Asn Gly
645 650 655

Glu Pro Val Asn Gly Arg His Thr Leu Gly Glu Asn Ile Ala Asp Asn
660 665 670

Gly Gly Leu Lys Ala Ala Tyr Arg Ala Tyr Gln Asn Trp Val Lys Lys
675 680 685

Asn Gly Ala Glu His Ser Leu Pro Thr Leu Gly Leu Thr Asn Asn Gln
690 695 700

Leu Phe Phe Leu Gly Phe Ala Gln Val Trp Cys Ser Val Arg Thr Pro
705 710 715 720

Glu Ser Ser His Glu Gly Leu Ile Thr Asp Pro His Ser Pro Ser Arg
725 730 735

Phe Arg Val Ile Gly Ser Leu Ser Asn Ser Lys Glu Phe Ser Glu His
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Phe Arg Cys Pro Pro Gly Ser Pro Met Asn Pro Pro His Lys Cys Glu
755 760 765

Val Trp
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gacgcgaggc tgccgggcta cccggccgag gcttcggggg cgcaaactaa tgggactggc 180

tcgctcggca gcatctcccc gctcttctaa gtacactgag cagggcccgc gctgaagtag 240

aagctgtccg ggggcgcgta gcccggagtc ccagtgtggc ccggaggaac ggagcccgtg 300

ccagggcggc ccagtcggga gcccggggac cgagcttgtg ctgtggggaa acccccactt 360

cttccaaggg acagcgatcc cgggacggtc gaggcgtcgg ggcggtcacc gagacctctg 420

cgggaagacc ccgtcgggga gagggcgcgc agccccgaag cgtctcggga agtcgagcgg 480

aatcgggcgg gatcacccgg gggcgcagag cccccgtcgc gcctcgtgcg gcagcggaga 540

gcccaggaga acgagccctc gggggccgaa gcccatgccc gggttggggg cggctgccca 600

gtgagtcctc ctggccggcc gggcggagaa gagcgacacc gaagccggcg ggaggggagc 660

acttcaaggc cggcggctgc ggaggatggg cgcctgagcg gctccgagcg cagcgcggca 720

gaggaaggcg aggcgagctt tggtgaggag gcgccaaggg atcccgaagt gcagtctgcc 780

cccgggaag atg gct cgg cct ggg cag cgt tgg ctc ggc aag tgg ctt gtg 831
Met Ala Arg Pro Gly Gln Arg Trp Leu Gly Lys Trp Leu Val
1 5 10

gcg atg gtc gtg tgg gcg ctg tgc cgg ctc gcc aca ccg ctg gcc aag 879
Ala Met Val Val Trp Ala Leu Cys Arg Leu Ala Thr Pro Leu Ala Lys
15 20 25 30

aac ctg gag ccc gta tcc tgg agc tcc ctc aac ccc aag ttc ctg agt 927
Asn Leu Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser
35 40 45

ggg aag ggc ttg gtg atc tat ccg aaa att gga gac aag ctg gac atc 975
Gly Lys Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile
50 55 60

atc tgc ccc cga gca gaa gca ggg cgg ccc tat gag tac tac aag ctg 1023
Ile Cys Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu
65 70 75

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tac ctg gtg cgg cct gag cag gca gct gcc tgt agc aca gtt ctc gac      1071
Tyr Leu Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp
    80                  85                  90

ccc aac gtg ttg gtc acc tgc aat agg cca gag cag gaa ata cgc ttt      1119
Pro Asn Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe
95                 100                 105                 110

acc atc aag ttc cag gag ttc agc ccc aac tac atg ggc ctg gag ttc      1167
Thr Ile Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe
                115                 120                 125

aag aag cac cat gat tac tac att acc tca aca tcc aat gga agc ctg      1215
Lys Lys His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu
            130                 135                 140

gag ggg ctg gaa aac cgg gag ggc ggt gtg tgc cgc aca cgc acc atg      1263
Glu Gly Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met
        145                 150                 155

aag atc atc atg aag gtt ggg caa gat ccc aat gct gtg acg cct gag      1311
Lys Ile Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu
    160                 165                 170

cag ctg act acc agc agg ccc agc aag gag gca gac aac act gtc aag      1359
Gln Leu Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys
175                 180                 185                 190

atg gcc aca cag gcc cct ggt agt cgg ggc tcc ctg ggt gac tct gat      1407
Met Ala Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp
                195                 200                 205

ggc aag cat gag act gtg aac cag gaa gag aag agt ggc cca ggt gca      1455
Gly Lys His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala
            210                 215                 220

agt ggg ggc agc agc ggg gac cct gat ggc ttc ttc aac tcc aag gtg      1503
Ser Gly Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys Val
        225                 230                 235

gca ttg ttc gcg gct gtc ggt gcc ggt tgc gtc atc ttc ctg ctc atc      1551
Ala Leu Phe Ala Ala Val Gly Ala Gly Cys Val Ile Phe Leu Leu Ile
    240                 245                 250

atc atc ttc ctg acg gtc cta cta ctg aag cta cgc aag cgg cac cgc      1599
Ile Ile Phe Leu Thr Val Leu Leu Leu Lys Leu Arg Lys Arg His Arg
255                 260                 265                 270

aag cac aca cag cag cgg gcg gct gcc ctc tcg ctc agt acc ctg gcc      1647
Lys His Thr Gln Gln Arg Ala Ala Ala Leu Ser Leu Ser Thr Leu Ala
                275                 280                 285

agt ccc aag ggg ggc agt ggc aca gcg ggc acc gag ccc agc gac atc      1695
Ser Pro Lys Gly Gly Ser Gly Thr Ala Gly Thr Glu Pro Ser Asp Ile
            290                 295                 300

atc att ccc tta cgg act aca gag aac aac tac tgc ccc cac tat gag      1743
Ile Ile Pro Leu Arg Thr Thr Glu Asn Asn Tyr Cys Pro His Tyr Glu
        305                 310                 315

aag gtg agt ggg gac tac ggg cac cct gtc tac atc gtc caa gag atg      1791
Lys Val Ser Gly Asp Tyr Gly His Pro Val Tyr Ile Val Gln Glu Met
    320                 325                 330

ccg ccc cag agc ccg gcg aac atc tac tac aag gtc tga gtgcccggca      1840
Pro Pro Gln Ser Pro Ala Asn Ile Tyr Tyr Lys Val
335                 340                 345

cggcctcagg cccccgaggg acagtcggcc tggaccggac ctctcctttc gcccccacac   1900

cccctccccc tgccagctgt gcccaccttt gtatttagtt ttgtagtttc ttggctttta   1960

taatcccccc ttttccctgc cccctgggct tcggaggggg gtgcttgtgc ccctaacccc   2020

catgctcttg tgccttcccc ctctggccag gcctctgggc tccgtggggg cgcccccttct  2080

tggaaggcag ggctggacac tgatggacag caggcaggga gacagtcccc tggccctgcc   2140

cctccctcgc ccccccttgcc accttcccag gactgcttgt ccgctatcat cactgttttt   2200
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aaaaaa 3346

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20 25 30

Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys
35 40 45

Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys
50 55 60

Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu
65 70 75 80

Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn
85 90 95

Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile
100 105 110

Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys
115 120 125

His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly
130 135 140

Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile
145 150 155 160

Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu
165 170 175

Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala
180 185 190

Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys
195 200 205

His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly
210 215 220

Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys Val Ala Leu
225 230 235 240

Phe Ala Ala Val Gly Ala Gly Cys Val Ile Phe Leu Leu Ile Ile Ile
245 250 255

Phe Leu Thr Val Leu Leu Leu Lys Leu Arg Lys Arg His Arg Lys His
260 265 270

Thr Gln Gln Arg Ala Ala Ala Leu Ser Leu Ser Thr Leu Ala Ser Pro
275 280 285

Lys Gly Gly Ser Gly Thr Ala Gly Thr Glu Pro Ser Asp Ile Ile Ile
290 295 300

Pro Leu Arg Thr Thr Glu Asn Asn Tyr Cys Pro His Tyr Glu Lys Val
305 310 315 320

Ser Gly Asp Tyr Gly His Pro Val Tyr Ile Val Gln Glu Met Pro Pro
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Gln Ser Pro Ala Asn Ile Tyr Tyr Lys Val
340 345

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gagatt atg acg ttg cag ccc cgc tgc gag gac gta gag acg gcc gag 168
Met Thr Leu Gln Pro Arg Cys Glu Asp Val Glu Thr Ala Glu
1 5 10

ggg gta gct tta act gtg acg ggt gtc gcc cag gtg aag atc atg acg 216
Gly Val Ala Leu Thr Val Thr Gly Val Ala Gln Val Lys Ile Met Thr
15 20 25 30

gag aag gaa ctc ctg gcc gtg gct tgt gag cag ttt ctg ggt aag aat 264

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Glu Lys Glu Leu Leu Ala Val Ala Cys Glu Gln Phe Leu Gly Lys Asn
                35                  40                  45

gtg cag gac atc aaa aac gtc gtc ctg cag acc ctg gag gga cat ctg      312
Val Gln Asp Ile Lys Asn Val Val Leu Gln Thr Leu Glu Gly His Leu
            50                  55                  60

cgc tcc atc ctc ggg acc ctg aca gtg gag cag att tat cag gac cgg      360
Arg Ser Ile Leu Gly Thr Leu Thr Val Glu Gln Ile Tyr Gln Asp Arg
        65                  70                  75

gac cag ttt gcc aag ctg gtg cgg gag gtg gca gcc cct gat gtt ggc      408
Asp Gln Phe Ala Lys Leu Val Arg Glu Val Ala Ala Pro Asp Val Gly
    80                  85                  90

cgc atg ggc att gag atc ctc agc ttc acc atc aag gac gtg tat gac      456
Arg Met Gly Ile Glu Ile Leu Ser Phe Thr Ile Lys Asp Val Tyr Asp
95                  100                 105                 110

aaa gtg gac tat ctg agc tcc ctg ggc aag acg cag act gcc gtg gtg      504
Lys Val Asp Tyr Leu Ser Ser Leu Gly Lys Thr Gln Thr Ala Val Val
                115                 120                 125

cag aga gat gct gac att ggc gtg gcc gag gct gaa cgg gac gca ggc      552
Gln Arg Asp Ala Asp Ile Gly Val Ala Glu Ala Glu Arg Asp Ala Gly
            130                 135                 140

atc cgg gaa gct gag tgc aag aag gag atg ctg gat gtg aag ttc atg      600
Ile Arg Glu Ala Glu Cys Lys Lys Glu Met Leu Asp Val Lys Phe Met
        145                 150                 155

gca gac acc aag att gct gac tct aag cga gcc ttc gag ctg caa aag      648
Ala Asp Thr Lys Ile Ala Asp Ser Lys Arg Ala Phe Glu Leu Gln Lys
    160                 165                 170

tca gcc ttc agt gag gag gtt aac atc aag aca gct gag gcc cag ttg      696
Ser Ala Phe Ser Glu Glu Val Asn Ile Lys Thr Ala Glu Ala Gln Leu
175                 180                 185                 190

gcc tat gag ctg cag ggg gcc cgt gaa cag cag aag atc cgg cag gaa      744
Ala Tyr Glu Leu Gln Gly Ala Arg Glu Gln Gln Lys Ile Arg Gln Glu
                195                 200                 205

gag att gag att gag gtt gtg cag cgc aag aaa cag att gcc gtg gag      792
Glu Ile Glu Ile Glu Val Val Gln Arg Lys Lys Gln Ile Ala Val Glu
            210                 215                 220

gca cag gag atc ctg cgt acg gac aag gag ctc atc gct aca gtg cgc      840
Ala Gln Glu Ile Leu Arg Thr Asp Lys Glu Leu Ile Ala Thr Val Arg
        225                 230                 235

cgg cct gcc gag gcc gag gcc cac cgc atc cag cag att gcc gag ggt      888
Arg Pro Ala Glu Ala Glu Ala His Arg Ile Gln Gln Ile Ala Glu Gly
    240                 245                 250

gaa aag gtg aag cag gtc ctc ttg gca cag gca gag gct gag aag atc      936
Glu Lys Val Lys Gln Val Leu Leu Ala Gln Ala Glu Ala Glu Lys Ile
255                 260                 265                 270

cgc aaa atc ggg gag gcg gaa gcg gca gtc atc gag gcg atg ggc aag      984
Arg Lys Ile Gly Glu Ala Glu Ala Ala Val Ile Glu Ala Met Gly Lys
                275                 280                 285

gca gag gct gag cgg atg aag ctc aag gca gaa gcc tac cag aaa tac     1032
Ala Glu Ala Glu Arg Met Lys Leu Lys Ala Glu Ala Tyr Gln Lys Tyr
            290                 295                 300

ggg gat gca gcc aag atg gcc ttg gtg cta gag gcc ctg ccc cag att     1080
Gly Asp Ala Ala Lys Met Ala Leu Val Leu Glu Ala Leu Pro Gln Ile
        305                 310                 315

gct gcc aaa atc gct gcc cca ctt acc aag gtc gat gag att gtg gtc     1128
Ala Ala Lys Ile Ala Ala Pro Leu Thr Lys Val Asp Glu Ile Val Val
    320                 325                 330

ctc agt gga gac aac agt aag gtc aca tca gaa gtg aac cga ctg ctg     1176
Leu Ser Gly Asp Asn Ser Lys Val Thr Ser Glu Val Asn Arg Leu Leu
335                 340                 345                 350

gcc gag ctg cct gcc tct gtg cat gcc ctc aca ggc gtg gac ctg tct     1224
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Ala Glu Leu Pro Ala Ser Val His Ala Leu Thr Gly Val Asp Leu Ser
355 360 365

aag ata ccc ctg atc aag aag gcc act ggt gtg cag gtg tga 1266
Lys Ile Pro Leu Ile Lys Lys Ala Thr Gly Val Gln Val
370 375

ggctcctaca ggcccactct cttcagcagc cacccggccc tccctccagc acccgtttta 1326
atcccacaga acaacgggaa cgttactgac tctggtgcct tatctcgaag ggaccagaag 1386
tgctgcgtgt tcaggccatc tctggctgtc ttcctgtctc tcctgtctgt ccacctcctc 1446
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aatggaggca gaagagccca ggacccaagc gtcttggcag gggtgctgtg aatgtccagt 2346
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Ala Leu Thr Val Thr Gly Val Ala Gln Val Lys Ile Met Thr Glu Lys
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Glu Leu Leu Ala Val Ala Cys Glu Gln Phe Leu Gly Lys Asn Val Gln
35 40 45

Asp Ile Lys Asn Val Val Leu Gln Thr Leu Glu Gly His Leu Arg Ser
50 55 60

Ile Leu Gly Thr Leu Thr Val Glu Gln Ile Tyr Gln Asp Arg Asp Gln
65 70 75 80

Phe Ala Lys Leu Val Arg Glu Val Ala Ala Pro Asp Val Gly Arg Met
85 90 95

Gly Ile Glu Ile Leu Ser Phe Thr Ile Lys Asp Val Tyr Asp Lys Val
100 105 110

Asp Tyr Leu Ser Ser Leu Gly Lys Thr Gln Thr Ala Val Val Gln Arg
115 120 125

Asp Ala Asp Ile Gly Val Ala Glu Ala Glu Arg Asp Ala Gly Ile Arg
130 135 140

Glu Ala Glu Cys Lys Lys Glu Met Leu Asp Val Lys Phe Met Ala Asp
145 150 155 160

Thr Lys Ile Ala Asp Ser Lys Arg Ala Phe Glu Leu Gln Lys Ser Ala
165 170 175

Phe Ser Glu Glu Val Asn Ile Lys Thr Ala Glu Ala Gln Leu Ala Tyr
180 185 190

Glu Leu Gln Gly Ala Arg Glu Gln Gln Lys Ile Arg Gln Glu Glu Ile
195 200 205

Glu Ile Glu Val Val Gln Arg Lys Lys Gln Ile Ala Val Glu Ala Gln
210 215 220

Glu Ile Leu Arg Thr Asp Lys Glu Leu Ile Ala Thr Val Arg Arg Pro
225 230 235 240

Ala Glu Ala Glu Ala His Arg Ile Gln Gln Ile Ala Glu Gly Glu Lys
245 250 255

Val Lys Gln Val Leu Leu Ala Gln Ala Glu Ala Glu Lys Ile Arg Lys
260 265 270

Ile Gly Glu Ala Glu Ala Ala Val Ile Glu Ala Met Gly Lys Ala Glu
275 280 285

Ala Glu Arg Met Lys Leu Lys Ala Glu Ala Tyr Gln Lys Tyr Gly Asp
290 295 300

Ala Ala Lys Met Ala Leu Val Leu Glu Ala Leu Pro Gln Ile Ala Ala
305 310 315 320

Lys Ile Ala Ala Pro Leu Thr Lys Val Asp Glu Ile Val Val Leu Ser
325 330 335

Gly Asp Asn Ser Lys Val Thr Ser Glu Val Asn Arg Leu Leu Ala Glu
340 345 350

Leu Pro Ala Ser Val His Ala Leu Thr Gly Val Asp Leu Ser Lys Ile
355 360 365

Pro Leu Ile Lys Lys Ala Thr Gly Val Gln Val
370 375

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<222> (7)..(1650)

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tgg act ctg ctg gtc tgc tgt ctg ctg acc cca ggt gtc cag ggg cag          96
Trp Thr Leu Leu Val Cys Cys Leu Leu Thr Pro Gly Val Gln Gly Gln
15                  20                  25                  30

gag ttc ctt ttg cgg gtg gag ccc cag aac cct gtg ctc tct gct gga         144
Glu Phe Leu Leu Arg Val Glu Pro Gln Asn Pro Val Leu Ser Ala Gly
                35                  40                  45

ggg tcc ctg ttt gtg aac tgc agt act gat tgt ccc agc tct gag aaa         192
Gly Ser Leu Phe Val Asn Cys Ser Thr Asp Cys Pro Ser Ser Glu Lys
            50                  55                  60

atc gcc ttg gag acg tcc cta tca aag gag ctg gtg gcc agt ggc atg         240
Ile Ala Leu Glu Thr Ser Leu Ser Lys Glu Leu Val Ala Ser Gly Met
        65                  70                  75

ggc tgg gca gcc ttc aat ctc agc aac gtg act ggc aac agt cgg atc         288
Gly Trp Ala Ala Phe Asn Leu Ser Asn Val Thr Gly Asn Ser Arg Ile
    80                  85                  90

ctc tgc tca gtg tac tgc aat ggc tcc cag ata aca ggc tcc tct aac         336
Leu Cys Ser Val Tyr Cys Asn Gly Ser Gln Ile Thr Gly Ser Ser Asn
95                  100                 105                 110

atc acc gtg tac agg ctc ccg gag cgt gtg gag ctg gca ccc ctg cct         384
Ile Thr Val Tyr Arg Leu Pro Glu Arg Val Glu Leu Ala Pro Leu Pro
                115                 120                 125

cct tgg cag ccg gtg ggc cag aac ttc acc ctg cgc tgc caa gtg gag         432
Pro Trp Gln Pro Val Gly Gln Asn Phe Thr Leu Arg Cys Gln Val Glu
            130                 135                 140

gat ggg tcg ccc cgg acc agc ctc acg gtg gtg ctg ctt cgc tgg gag         480
Asp Gly Ser Pro Arg Thr Ser Leu Thr Val Val Leu Leu Arg Trp Glu
        145                 150                 155

gag gag ctg agc cgg cag ccc gca gtg gag gag cca gcg gag gtc act         528
Glu Glu Leu Ser Arg Gln Pro Ala Val Glu Glu Pro Ala Glu Val Thr
    160                 165                 170

gcc act gtg ctg gcc agc aga gac gac cac gga gcc cct ttc tca tgc         576
Ala Thr Val Leu Ala Ser Arg Asp Asp His Gly Ala Pro Phe Ser Cys
175                 180                 185                 190

cgc aca gaa ctg gac atg cag ccc cag ggg ctg gga ctg ttc gtg aac         624
Arg Thr Glu Leu Asp Met Gln Pro Gln Gly Leu Gly Leu Phe Val Asn
                195                 200                 205

acc tca gcc ccc cgc cag ctc cga acc ttt gtc ctg ccc gtg acc ccc         672
Thr Ser Ala Pro Arg Gln Leu Arg Thr Phe Val Leu Pro Val Thr Pro
            210                 215                 220

ccg cgc ctc gtg gcc ccc cgg ttc ttg gag gtg gaa acg tcg tgg ccg         720
Pro Arg Leu Val Ala Pro Arg Phe Leu Glu Val Glu Thr Ser Trp Pro
        225                 230                 235

gtg gac tgc acc cta gac ggg ctt ttt cca gcc tca gag gcc cag gtc         768
Val Asp Cys Thr Leu Asp Gly Leu Phe Pro Ala Ser Glu Ala Gln Val
    240                 245                 250

tac ctg gcg ctg ggg gac cag atg ctg aat gcg aca gtc atg aac cac         816
Tyr Leu Ala Leu Gly Asp Gln Met Leu Asn Ala Thr Val Met Asn His
255                 260                 265                 270

ggg gac acg cta acg gcc aca gcc aca gcc acg gcg cgc gcg gat cag         864
Gly Asp Thr Leu Thr Ala Thr Ala Thr Ala Thr Ala Arg Ala Asp Gln
                275                 280                 285

gag ggt gcc cgg gag atc gtc tgc aac gtg acc cta ggg ggc gag aga         912
Glu Gly Ala Arg Glu Ile Val Cys Asn Val Thr Leu Gly Gly Glu Arg
            290                 295                 300

cgg gag gcc cgg gag aac ttg acg gtc ttt agc ttc cta gga ccc att         960
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Arg Glu Ala Arg Glu Asn Leu Thr Val Phe Ser Phe Leu Gly Pro Ile
305                 310                 315

gtg aac ctc agc gag ccc acc gcc cat gag ggg tcc aca gtg acc gtg      1008
Val Asn Leu Ser Glu Pro Thr Ala His Glu Gly Ser Thr Val Thr Val
320                 325                 330

agt tgc atg gct ggg gct cga gtc cag gtc acg ctg gac gga gtt ccg      1056
Ser Cys Met Ala Gly Ala Arg Val Gln Val Thr Leu Asp Gly Val Pro
335                 340                 345                 350

gcc gcg gcc ccg ggg cag cca gct caa ctt cag cta aat gct acc gag      1104
Ala Ala Ala Pro Gly Gln Pro Ala Gln Leu Gln Leu Asn Ala Thr Glu
                355                 360                 365

agt gac gac gga cgc agc ttc ttc tgc agt gcc act ctc gag gtg gac      1152
Ser Asp Asp Gly Arg Ser Phe Phe Cys Ser Ala Thr Leu Glu Val Asp
            370                 375                 380

ggc gag ttc ttg cac agg aac agt agc gtc cag ctg cga gtc ctg tat      1200
Gly Glu Phe Leu His Arg Asn Ser Ser Val Gln Leu Arg Val Leu Tyr
385                 390                 395

ggt ccc aaa att gac cga gcc aca tgc ccc cag cac ttg aaa tgg aaa      1248
Gly Pro Lys Ile Asp Arg Ala Thr Cys Pro Gln His Leu Lys Trp Lys
400                 405                 410

gat aaa acg aga cac gtc ctg cag tgc caa gcc agg ggc aac ccg tac      1296
Asp Lys Thr Arg His Val Leu Gln Cys Gln Ala Arg Gly Asn Pro Tyr
415                 420                 425                 430

ccc gag ctg cgg tgt ttg aag gaa ggc tcc agc cgg gag gtg ccg gtg      1344
Pro Glu Leu Arg Cys Leu Lys Glu Gly Ser Ser Arg Glu Val Pro Val
                435                 440                 445

ggg atc ccg ttc ttc gtc aac gta aca cat aat ggt act tat cag tgc      1392
Gly Ile Pro Phe Phe Val Asn Val Thr His Asn Gly Thr Tyr Gln Cys
            450                 455                 460

caa gcg tcc agc tca cga ggc aaa tac acc ctg gtc gtg gtg atg gac      1440
Gln Ala Ser Ser Ser Arg Gly Lys Tyr Thr Leu Val Val Val Met Asp
465                 470                 475

att gag gct ggg agc tcc cac ttt gtc ccc gtc ttc gtg gcg gtg tta      1488
Ile Glu Ala Gly Ser Ser His Phe Val Pro Val Phe Val Ala Val Leu
480                 485                 490

ctg acc ctg ggc gtg gtg act atc gta ctg gcc tta atg tac gtc ttc      1536
Leu Thr Leu Gly Val Val Thr Ile Val Leu Ala Leu Met Tyr Val Phe
495                 500                 505                 510

agg gag cac caa cgg agc ggc agt tac cat gtt agg gag gag agc acc      1584
Arg Glu His Gln Arg Ser Gly Ser Tyr His Val Arg Glu Glu Ser Thr
                515                 520                 525

tat ctg ccc ctc acg tct atg cag ccg aca gaa gca atg ggg gaa gaa      1632
Tyr Leu Pro Leu Thr Ser Met Gln Pro Thr Glu Ala Met Gly Glu Glu
            530                 535                 540

ccg tcc aga gct gag tga cgctgggatc cgggatcaaa gttggcgggg            1680
Pro Ser Arg Ala Glu
545

gcttggctgt gccctcagat tccgcaccaa taaagccttc aaactcccta aaaaaaaaaa   1740

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a                                  1771

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<213>  Homo sapiens

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Met Ala Thr Met Val Pro Ser Val Leu Trp Pro Arg Ala Cys Trp Thr
1               5                   10                  15

Leu Leu Val Cys Cys Leu Leu Thr Pro Gly Val Gln Gly Gln Glu Phe
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20 25 30

Leu Leu Arg Val Glu Pro Gln Asn Pro Val Leu Ser Ala Gly Gly Ser
35 40 45

Leu Phe Val Asn Cys Ser Thr Asp Cys Pro Ser Ser Glu Lys Ile Ala
50 55 60

Leu Glu Thr Ser Leu Ser Lys Glu Leu Val Ala Ser Gly Met Gly Trp
65 70 75 80

Ala Ala Phe Asn Leu Ser Asn Val Thr Gly Asn Ser Arg Ile Leu Cys
85 90 95

Ser Val Tyr Cys Asn Gly Ser Gln Ile Thr Gly Ser Ser Asn Ile Thr
100 105 110

Val Tyr Arg Leu Pro Glu Arg Val Glu Leu Ala Pro Leu Pro Pro Trp
115 120 125

Gln Pro Val Gly Gln Asn Phe Thr Leu Arg Cys Gln Val Glu Asp Gly
130 135 140

Ser Pro Arg Thr Ser Leu Thr Val Val Leu Leu Arg Trp Glu Glu Glu
145 150 155 160

Leu Ser Arg Gln Pro Ala Val Glu Glu Pro Ala Glu Val Thr Ala Thr
165 170 175

Val Leu Ala Ser Arg Asp Asp His Gly Ala Pro Phe Ser Cys Arg Thr
180 185 190

Glu Leu Asp Met Gln Pro Gln Gly Leu Gly Leu Phe Val Asn Thr Ser
195 200 205

Ala Pro Arg Gln Leu Arg Thr Phe Val Leu Pro Val Thr Pro Pro Arg
210 215 220

Leu Val Ala Pro Arg Phe Leu Glu Val Glu Thr Ser Trp Pro Val Asp
225 230 235 240

Cys Thr Leu Asp Gly Leu Phe Pro Ala Ser Glu Ala Gln Val Tyr Leu
245 250 255

Ala Leu Gly Asp Gln Met Leu Asn Ala Thr Val Met Asn His Gly Asp
260 265 270

Thr Leu Thr Ala Thr Ala Thr Ala Thr Ala Arg Ala Asp Gln Glu Gly
275 280 285

Ala Arg Glu Ile Val Cys Asn Val Thr Leu Gly Gly Glu Arg Arg Glu
290 295 300

Ala Arg Glu Asn Leu Thr Val Phe Ser Phe Leu Gly Pro Ile Val Asn
305 310 315 320

Leu Ser Glu Pro Thr Ala His Glu Gly Ser Thr Val Thr Val Ser Cys
325 330 335

Met Ala Gly Ala Arg Val Gln Val Thr Leu Asp Gly Val Pro Ala Ala

340 345 350

Ala Pro Gly Gln Pro Ala Gln Leu Gln Leu Asn Ala Thr Glu Ser Asp
355 360 365

Asp Gly Arg Ser Phe Phe Cys Ser Ala Thr Leu Glu Val Asp Gly Glu
370 375 380

Phe Leu His Arg Asn Ser Ser Val Gln Leu Arg Val Leu Tyr Gly Pro
385 390 395 400

Lys Ile Asp Arg Ala Thr Cys Pro Gln His Leu Lys Trp Lys Asp Lys
405 410 415

Thr Arg His Val Leu Gln Cys Gln Ala Arg Gly Asn Pro Tyr Pro Glu
420 425 430

Leu Arg Cys Leu Lys Glu Gly Ser Ser Arg Glu Val Pro Val Gly Ile
435 440 445

Pro Phe Phe Val Asn Val Thr His Asn Gly Thr Tyr Gln Cys Gln Ala
450 455 460

Ser Ser Ser Arg Gly Lys Tyr Thr Leu Val Val Val Met Asp Ile Glu
465 470 475 480

Ala Gly Ser Ser His Phe Val Pro Val Phe Val Ala Val Leu Leu Thr
485 490 495

Leu Gly Val Val Thr Ile Val Leu Ala Leu Met Tyr Val Phe Arg Glu
500 505 510

His Gln Arg Ser Gly Ser Tyr His Val Arg Glu Glu Ser Thr Tyr Leu
515 520 525

Pro Leu Thr Ser Met Gln Pro Thr Glu Ala Met Gly Glu Glu Pro Ser
530 535 540

Arg Ala Glu
545

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ggctgctaac tgcgccacct gctgcagcct gtccccgccg ctctgaagcg gccgcgtcga 120

agccgaa atg ccg cca ccc cgg acc ggc cga ggc ctt ctc tgg ctg ggt 169
Met Pro Pro Pro Arg Thr Gly Arg Gly Leu Leu Trp Leu Gly
1 5 10

ctg gtt ctg agc tcc gtc tgc gtc gcc ctc gga tcc gaa acg cag gcc 217
Leu Val Leu Ser Ser Val Cys Val Ala Leu Gly Ser Glu Thr Gln Ala
15 20 25 30

aac tcg acc aca gat gct ctg aac gtt ctt ctc atc atc gtg gat gac 265
Asn Ser Thr Thr Asp Ala Leu Asn Val Leu Leu Ile Ile Val Asp Asp

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                35                  40                  45

ctg cgc ccc tcc ctg ggc tgt tat ggg gat aag ctg gtg agg tcc cca      313
Leu Arg Pro Ser Leu Gly Cys Tyr Gly Asp Lys Leu Val Arg Ser Pro
            50                  55                  60

aat att gac caa ctg gca tcc cac agc ctc ctc ttc cag aat gcc ttt      361
Asn Ile Asp Gln Leu Ala Ser His Ser Leu Leu Phe Gln Asn Ala Phe
        65                  70                  75

gcg cag caa gca gtg tgc gcc ccg agc cgc gtt tct ttc ctc act ggc      409
Ala Gln Gln Ala Val Cys Ala Pro Ser Arg Val Ser Phe Leu Thr Gly
    80                  85                  90

agg aga cct gac acc acc cgc ctg tac gac ttc aac tcc tac tgg agg      457
Arg Arg Pro Asp Thr Thr Arg Leu Tyr Asp Phe Asn Ser Tyr Trp Arg
95                  100                 105                 110

gtg cac gct gga aac ttc tcc acc atc ccc cag tac ttc aag gag aat      505
Val His Ala Gly Asn Phe Ser Thr Ile Pro Gln Tyr Phe Lys Glu Asn
                115                 120                 125

ggc tat gtg acc atg tcg gtg gga aaa gtc ttt cac cct ggg ata tct      553
Gly Tyr Val Thr Met Ser Val Gly Lys Val Phe His Pro Gly Ile Ser
            130                 135                 140

tct aac cat acc gat gat tct ccg tat agc tgg tct ttt cca cct tat      601
Ser Asn His Thr Asp Asp Ser Pro Tyr Ser Trp Ser Phe Pro Pro Tyr
        145                 150                 155

cat cct tcc tct gag aag tat gaa aac act aag aca tgt cga ggg cca      649
His Pro Ser Ser Glu Lys Tyr Glu Asn Thr Lys Thr Cys Arg Gly Pro
    160                 165                 170

gat gga gaa ctc cat gcc aac ctg ctt tgc cct gtg gat gtg ctg gat      697
Asp Gly Glu Leu His Ala Asn Leu Leu Cys Pro Val Asp Val Leu Asp
175                 180                 185                 190

gtt ccc gag ggc acc ttg cct gac aaa cag agc act gag caa gcc ata      745
Val Pro Glu Gly Thr Leu Pro Asp Lys Gln Ser Thr Glu Gln Ala Ile
                195                 200                 205

cag ttg ttg gaa aag atg aaa acg tca gcc agt cct ttc ttc ctg gcc      793
Gln Leu Leu Glu Lys Met Lys Thr Ser Ala Ser Pro Phe Phe Leu Ala
            210                 215                 220

gtt ggg tat cat aag cca cac atc ccc ttc aga tac ccc aag gaa ttt      841
Val Gly Tyr His Lys Pro His Ile Pro Phe Arg Tyr Pro Lys Glu Phe
        225                 230                 235

cag aag ttg tat ccc ttg gag aac atc acc ctg gcc ccc gat ccc gag      889
Gln Lys Leu Tyr Pro Leu Glu Asn Ile Thr Leu Ala Pro Asp Pro Glu
    240                 245                 250

gtc cct gat ggc cta ccc cct gtg gcc tac aac ccc tgg atg gac atc      937
Val Pro Asp Gly Leu Pro Pro Val Ala Tyr Asn Pro Trp Met Asp Ile
255                 260                 265                 270

agg caa cgg gaa gac gtc caa gcc tta aac atc agt gtg ccg tat ggt      985
Arg Gln Arg Glu Asp Val Gln Ala Leu Asn Ile Ser Val Pro Tyr Gly
                275                 280                 285

cca att cct gtg gac ttt cag cgg aaa atc cgc cag agc tac ttt gcc     1033
Pro Ile Pro Val Asp Phe Gln Arg Lys Ile Arg Gln Ser Tyr Phe Ala
            290                 295                 300

tct gtg tca tat ttg gat aca cag gtc ggc cgc ctc ttg agt gct ttg     1081
Ser Val Ser Tyr Leu Asp Thr Gln Val Gly Arg Leu Leu Ser Ala Leu
        305                 310                 315

gac gat ctt cag ctg gcc aac agc acc atc att gca ttt acc tcg gat     1129
Asp Asp Leu Gln Leu Ala Asn Ser Thr Ile Ile Ala Phe Thr Ser Asp
    320                 325                 330

cat ggt ttc ctc atg agg aca aat acc tga ttttgaataa agcagcattc      1179
His Gly Phe Leu Met Arg Thr Asn Thr
335                 340

agttgaaata acccttttctg tggtaattcc aagtgaatat ttttcttcta ggtgatgagt  1239
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ttctacttcc tctggttttt acaacaggaa atgaaatggt atctaaaata aacaagctgt 1299

ggtatgatga taatt 1314

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<400> 36

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20 25 30

Thr Thr Asp Ala Leu Asn Val Leu Leu Ile Ile Val Asp Asp Leu Arg
35 40 45

Pro Ser Leu Gly Cys Tyr Gly Asp Lys Leu Val Arg Ser Pro Asn Ile
50 55 60

Asp Gln Leu Ala Ser His Ser Leu Leu Phe Gln Asn Ala Phe Ala Gln
65 70 75 80

Gln Ala Val Cys Ala Pro Ser Arg Val Ser Phe Leu Thr Gly Arg Arg
85 90 95

Pro Asp Thr Thr Arg Leu Tyr Asp Phe Asn Ser Tyr Trp Arg Val His
100 105 110

Ala Gly Asn Phe Ser Thr Ile Pro Gln Tyr Phe Lys Glu Asn Gly Tyr
115 120 125

Val Thr Met Ser Val Gly Lys Val Phe His Pro Gly Ile Ser Ser Asn
130 135 140

His Thr Asp Asp Ser Pro Tyr Ser Trp Ser Phe Pro Pro Tyr His Pro
145 150 155 160

Ser Ser Glu Lys Tyr Glu Asn Thr Lys Thr Cys Arg Gly Pro Asp Gly
165 170 175

Glu Leu His Ala Asn Leu Leu Cys Pro Val Asp Val Leu Asp Val Pro
180 185 190

Glu Gly Thr Leu Pro Asp Lys Gln Ser Thr Glu Gln Ala Ile Gln Leu
195 200 205

Leu Glu Lys Met Lys Thr Ser Ala Ser Pro Phe Phe Leu Ala Val Gly
210 215 220

Tyr His Lys Pro His Ile Pro Phe Arg Tyr Pro Lys Glu Phe Gln Lys
225 230 235 240

Leu Tyr Pro Leu Glu Asn Ile Thr Leu Ala Pro Asp Pro Glu Val Pro
245 250 255

Asp Gly Leu Pro Pro Val Ala Tyr Asn Pro Trp Met Asp Ile Arg Gln
260 265 270

Arg Glu Asp Val Gln Ala Leu Asn Ile Ser Val Pro Tyr Gly Pro Ile
275 280 285

Pro Val Asp Phe Gln Arg Lys Ile Arg Gln Ser Tyr Phe Ala Ser Val
290 295 300

Ser Tyr Leu Asp Thr Gln Val Gly Arg Leu Leu Ser Ala Leu Asp Asp
305 310 315 320

Leu Gln Leu Ala Asn Ser Thr Ile Ile Ala Phe Thr Ser Asp His Gly
325 330 335

Phe Leu Met Arg Thr Asn Thr
340

<210> 37
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<222> (405)..(4121)
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cttcaccgcc gccgccgtcg ccgccgggtg ggagccgggc cgggcagccg gagcgcggcc 180

gccagcgagc cggagctgcc gccgcccctg cacgcccgcc gcccaggccc gcgcgccgcg 240

gcgctgcgct cgaccccgcc cgcgccgccg ccgccgccgc ctctgccgct gccgctgcct 300

ctgcgggcgc tcggagggcg ggcgggcgct gggaggccgg cgcggcggct gggagccggg 360

cgcgggcggc ggcggcgggg ccgggcgggc gggtcgcggg ggca atg cgg gcg cag 416
Met Arg Ala Gln
1

ggc cgg ggg cgc ctt ccc cgg cgg ctg ctg ctg ctg ctg gcg ctc tgg 464
Gly Arg Gly Arg Leu Pro Arg Arg Leu Leu Leu Leu Leu Ala Leu Trp
5 10 15 20

gtg cag gcg gcg cgg ccc atg ggc tat ttc gag ctg cag ctg agc gcg 512
Val Gln Ala Ala Arg Pro Met Gly Tyr Phe Glu Leu Gln Leu Ser Ala
25 30 35

ctg cgg aac gtg aac ggg gag ctg ctg agc ggc gcc tgc tgt gac ggc 560
Leu Arg Asn Val Asn Gly Glu Leu Leu Ser Gly Ala Cys Cys Asp Gly
40 45 50

gac ggc cgg aca acg cgc gcg ggg ggc tgc ggc cac gac gag tgc gac 608
Asp Gly Arg Thr Thr Arg Ala Gly Gly Cys Gly His Asp Glu Cys Asp
55 60 65

acg tac gtg cgc gtg tgc ctt aag gag tac cag gcc aag gtg acg ccc 656
Thr Tyr Val Arg Val Cys Leu Lys Glu Tyr Gln Ala Lys Val Thr Pro
70 75 80

acg ggg ccc tgc agc tac ggc cac ggc gcc acg ccc gtg ctg ggc ggc 704
Thr Gly Pro Cys Ser Tyr Gly His Gly Ala Thr Pro Val Leu Gly Gly
85 90 95 100

aac tcc ttc tac ctg ccg ccg gcg ggc gct gcg ggg gac cga gcg cgg 752
Asn Ser Phe Tyr Leu Pro Pro Ala Gly Ala Ala Gly Asp Arg Ala Arg
105 110 115

gcg cgg gcc cgg gcc ggc ggc gac cag gac ccg ggc ctc gtc gtc atc 800
Ala Arg Ala Arg Ala Gly Gly Asp Gln Asp Pro Gly Leu Val Val Ile
120 125 130

ccc ttc cag ttc gcc tgg ccg cgc tcc ttt acc ctc atc gtg gag gcc 848

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Pro Phe Gln Phe Ala Trp Pro Arg Ser Phe Thr Leu Ile Val Glu Ala
        135                 140                 145

tgg gac tgg gac aac gat acc acc ccg aat gag gag ctg ctg atc gag      896
Trp Asp Trp Asp Asn Asp Thr Thr Pro Asn Glu Glu Leu Leu Ile Glu
    150                 155                 160

cga gtg tcg cat gcc ggc atg atc aac ccg gag gac cgc tgg aag agc      944
Arg Val Ser His Ala Gly Met Ile Asn Pro Glu Asp Arg Trp Lys Ser
165                 170                 175                 180

ctg cac ttc agc ggc cac gtg gcg cac ctg gag ctg cag atc cgc gtg      992
Leu His Phe Ser Gly His Val Ala His Leu Glu Leu Gln Ile Arg Val
                185                 190                 195

cgc tgc gac gag aac tac tac agc gcc act tgc aac aag ttc tgc cgg     1040
Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn Lys Phe Cys Arg
            200                 205                 210

ccc cgc aac gac ttt ttc ggc cac tac acc tgc gac cag tac ggc aac     1088
Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp Gln Tyr Gly Asn
        215                 220                 225

aag gcc tgc atg gac ggc tgg atg ggc aag gag tgc aag gaa gct gtg     1136
Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys Lys Glu Ala Val
    230                 235                 240

tgt aaa caa ggg tgt aat ttg ctc cac ggg gga tgc acc gtg cct ggg     1184
Cys Lys Gln Gly Cys Asn Leu Leu His Gly Gly Cys Thr Val Pro Gly
245                 250                 255                 260

gag tgc agg tgc agc tac ggc tgg caa ggg agg ttc tgc gat gag tgt     1232
Glu Cys Arg Cys Ser Tyr Gly Trp Gln Gly Arg Phe Cys Asp Glu Cys
                265                 270                 275

gtc ccc tac ccc ggc tgc gtg cat ggc agt tgt gtg gag ccc tgg cag     1280
Val Pro Tyr Pro Gly Cys Val His Gly Ser Cys Val Glu Pro Trp Gln
            280                 285                 290

tgc aac tgt gag acc aac tgg ggc ggc ctg ctc tgt gac aaa gac ctg     1328
Cys Asn Cys Glu Thr Asn Trp Gly Gly Leu Leu Cys Asp Lys Asp Leu
        295                 300                 305

aac tac tgt ggc agc cac cac ccc tgc acc aac gga ggc acg tgc atc     1376
Asn Tyr Cys Gly Ser His His Pro Cys Thr Asn Gly Gly Thr Cys Ile
    310                 315                 320

aac gcc gag cct gac cag tac cgc tgc acc tgc cct gac ggc tac tcg     1424
Asn Ala Glu Pro Asp Gln Tyr Arg Cys Thr Cys Pro Asp Gly Tyr Ser
325                 330                 335                 340

ggc agg aac tgt gag aag gct gag cac gcc tgc acc tcc aac ccg tgt     1472
Gly Arg Asn Cys Glu Lys Ala Glu His Ala Cys Thr Ser Asn Pro Cys
                345                 350                 355

gcc aac ggg ggc tct tgc cat gag gtg ccg tcc ggc ttc gaa tgc cac     1520
Ala Asn Gly Gly Ser Cys His Glu Val Pro Ser Gly Phe Glu Cys His
            360                 365                 370

tgc cca tcg ggc tgg agc ggg ccc acc tgt gcc ctt gac atc gat gag     1568
Cys Pro Ser Gly Trp Ser Gly Pro Thr Cys Ala Leu Asp Ile Asp Glu
        375                 380                 385

tgt gct tcg aac ccg tgt gcg gcc ggt ggc acc tgt gtg gac cag gtg     1616
Cys Ala Ser Asn Pro Cys Ala Ala Gly Gly Thr Cys Val Asp Gln Val
    390                 395                 400

gac ggc ttt gag tgc atc tgc ccc gag cag tgg gtg ggg gcc acc tgc     1664
Asp Gly Phe Glu Cys Ile Cys Pro Glu Gln Trp Val Gly Ala Thr Cys
405                 410                 415                 420

cag ctg gac gcc aat gag tgt gaa ggg aag cca tgc ctt aac gct ttt     1712
Gln Leu Asp Ala Asn Glu Cys Glu Gly Lys Pro Cys Leu Asn Ala Phe
                425                 430                 435

tct tgc aaa aac ctg att ggc ggc tat tac tgt gat tgc atc ccg ggc     1760
Ser Cys Lys Asn Leu Ile Gly Gly Tyr Tyr Cys Asp Cys Ile Pro Gly
            440                 445                 450

tgg aag ggc atc aac tgc cat atc aac gtc aac gac tgt cgc ggg cag     1808
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Trp Lys Gly Ile Asn Cys His Ile Asn Val Asn Asp Cys Arg Gly Gln
          455                 460                 465

tgt cag cat ggg ggc acc tgc aag gac ctg gtg aac ggg tac cag tgt      1856
Cys Gln His Gly Gly Thr Cys Lys Asp Leu Val Asn Gly Tyr Gln Cys
    470                 475                 480

gtg tgc cca cgg ggc ttc gga ggc cgg cat tgc gag ctg gaa cga gac      1904
Val Cys Pro Arg Gly Phe Gly Gly Arg His Cys Glu Leu Glu Arg Asp
485                 490                 495                 500

gag tgt gcc agc agc ccc tgc cac agc ggc ggc ctc tgc gag gac ctg      1952
Glu Cys Ala Ser Ser Pro Cys His Ser Gly Gly Leu Cys Glu Asp Leu
                505                 510                 515

gcc gac ggc ttc cac tgc cac tgc ccc cag ggc ttc tcc ggg cct ctc      2000
Ala Asp Gly Phe His Cys His Cys Pro Gln Gly Phe Ser Gly Pro Leu
            520                 525                 530

tgt gag gtg gat gtc gac ctt tgt gag cca agc ccc tgc cgg aac ggc      2048
Cys Glu Val Asp Val Asp Leu Cys Glu Pro Ser Pro Cys Arg Asn Gly
        535                 540                 545

gct cgc tgc tat aac ctg gag ggt gac tat tac tgc gcc tgc cct gat      2096
Ala Arg Cys Tyr Asn Leu Glu Gly Asp Tyr Tyr Cys Ala Cys Pro Asp
    550                 555                 560

gac ttt ggt ggc aag aac tgc tcc gtg ccc cgc gag ccg tgc cct ggc      2144
Asp Phe Gly Gly Lys Asn Cys Ser Val Pro Arg Glu Pro Cys Pro Gly
565                 570                 575                 580

ggg gcc tgc aga gtg atc gat ggc tgc ggg tca gac gcg ggg cct ggg      2192
Gly Ala Cys Arg Val Ile Asp Gly Cys Gly Ser Asp Ala Gly Pro Gly
                585                 590                 595

atg cct ggc aca gca gcc tcc ggc gtg tgt ggc ccc cat gga cgc tgc      2240
Met Pro Gly Thr Ala Ala Ser Gly Val Cys Gly Pro His Gly Arg Cys
            600                 605                 610

gtc agc cag cca ggg ggc aac ttt tcc tgc atc tgt gac agt ggc ttt      2288
Val Ser Gln Pro Gly Gly Asn Phe Ser Cys Ile Cys Asp Ser Gly Phe
        615                 620                 625

act ggc acc tac tgc cat gag aac att gac gac tgc ctg ggc cag ccc      2336
Thr Gly Thr Tyr Cys His Glu Asn Ile Asp Asp Cys Leu Gly Gln Pro
    630                 635                 640

tgc cgc aat ggg ggc aca tgc atc gat gag gtg gac gcc ttc cgc tgc      2384
Cys Arg Asn Gly Gly Thr Cys Ile Asp Glu Val Asp Ala Phe Arg Cys
645                 650                 655                 660

ttc tgc ccc agc ggc tgg gag ggc gag ctc tgc gac acc aat ccc aac      2432
Phe Cys Pro Ser Gly Trp Glu Gly Glu Leu Cys Asp Thr Asn Pro Asn
                665                 670                 675

gac tgc ctt ccc gat ccc tgc cac agc cgc ggc cgc tgc tac gac ctg      2480
Asp Cys Leu Pro Asp Pro Cys His Ser Arg Gly Arg Cys Tyr Asp Leu
            680                 685                 690

gtc aat gac ttc tac tgt gcg tgc gac gac ggc tgg aag ggc aag acc      2528
Val Asn Asp Phe Tyr Cys Ala Cys Asp Asp Gly Trp Lys Gly Lys Thr
        695                 700                 705

tgc cac tca cgc gag ttc cag tgc gat gcc tac acc tgc agc aac ggt      2576
Cys His Ser Arg Glu Phe Gln Cys Asp Ala Tyr Thr Cys Ser Asn Gly
    710                 715                 720

ggc acc tgc tac gac agc ggc gac acc ttc cgc tgc gcc tgc ccc ccc      2624
Gly Thr Cys Tyr Asp Ser Gly Asp Thr Phe Arg Cys Ala Cys Pro Pro
725                 730                 735                 740

ggc tgg aag ggc agc acc tgc gcc gtc gcc aag aac agc agc tgc ctg      2672
Gly Trp Lys Gly Ser Thr Cys Ala Val Ala Lys Asn Ser Ser Cys Leu
                745                 750                 755

ccc aac ccc tgt gtg aat ggt ggc acc tgc gtg ggc agc ggg gcc tcc      2720
Pro Asn Pro Cys Val Asn Gly Gly Thr Cys Val Gly Ser Gly Ala Ser
            760                 765                 770

ttc tcc tgc atc tgc cgg gac ggc tgg gag ggt cgt act tgc act cac      2768
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Phe Ser Cys Ile Cys Arg Asp Gly Trp Glu Gly Arg Thr Cys Thr His
        775                 780                 785

aat acc aac gac tgc aac cct ctg cct tgc tac aat ggt ggc atc tgt      2816
Asn Thr Asn Asp Cys Asn Pro Leu Pro Cys Tyr Asn Gly Gly Ile Cys
    790                 795                 800

gtt gac ggc gtc aac tgg ttc cgc tgc gag tgt gca cct ggc ttc gcg      2864
Val Asp Gly Val Asn Trp Phe Arg Cys Glu Cys Ala Pro Gly Phe Ala
805                 810                 815                 820

ggg cct gac tgc cgc atc aac atc gac gag tgc cag tcc tcg ccc tgt      2912
Gly Pro Asp Cys Arg Ile Asn Ile Asp Glu Cys Gln Ser Ser Pro Cys
                825                 830                 835

gcc tac ggg gcc acg tgt gtg gat gag atc aac ggg tat cgc tgt agc      2960
Ala Tyr Gly Ala Thr Cys Val Asp Glu Ile Asn Gly Tyr Arg Cys Ser
            840                 845                 850

tgc cca ccc ggc cga gcc ggc ccc cgg tgc cag gaa gtg atc ggg ttc      3008
Cys Pro Pro Gly Arg Ala Gly Pro Arg Cys Gln Glu Val Ile Gly Phe
        855                 860                 865

ggg aga tcc tgc tgg tcc cgg ggc act ccg ttc cca cac gga agc tcc      3056
Gly Arg Ser Cys Trp Ser Arg Gly Thr Pro Phe Pro His Gly Ser Ser
    870                 875                 880

tgg gtg gaa gac tgc aac agc tgc cgc tgc ctg gat ggc cgc cgt gac      3104
Trp Val Glu Asp Cys Asn Ser Cys Arg Cys Leu Asp Gly Arg Arg Asp
885                 890                 895                 900

tgc agc aag gtg tgg tgc gga tgg aag cct tgt ctg ctg gcc ggc cag      3152
Cys Ser Lys Val Trp Cys Gly Trp Lys Pro Cys Leu Leu Ala Gly Gln
                905                 910                 915

ccc gag gcc ctg agc gcc cag tgc cca ctg ggg caa agg tgc ctg gag      3200
Pro Glu Ala Leu Ser Ala Gln Cys Pro Leu Gly Gln Arg Cys Leu Glu
            920                 925                 930

aag gcc cca ggc cag tgt ctg cga cca ccc tgt gag gcc tgg ggg gag      3248
Lys Ala Pro Gly Gln Cys Leu Arg Pro Pro Cys Glu Ala Trp Gly Glu
        935                 940                 945

tgc ggc gca gaa gag cca ccg agc acc ccc tgc ctg cca cgc tcc ggc      3296
Cys Gly Ala Glu Glu Pro Pro Ser Thr Pro Cys Leu Pro Arg Ser Gly
    950                 955                 960

cac ctg gac aat aac tgt gcc cgc ctc acc ttg cat ttc aac cgt gac      3344
His Leu Asp Asn Asn Cys Ala Arg Leu Thr Leu His Phe Asn Arg Asp
965                 970                 975                 980

cac gtg ccc cag ggc acc acg gtg ggc gcc att tgc tcc ggg atc cgc      3392
His Val Pro Gln Gly Thr Thr Val Gly Ala Ile Cys Ser Gly Ile Arg
                985                 990                 995

tcc ctg cca gcc  aca agg gct gtg gca  cgg gac cgc ctg ctg  gtg      3437
Ser Leu Pro Ala  Thr Arg Ala Val Ala  Arg Asp Arg Leu Leu  Val
            1000                1005                1010

ttg ctt tgc gac  cgg gcg tcc tcg ggg  gcc agt gcc gtg gag  gtg      3482
Leu Leu Cys Asp  Arg Ala Ser Ser Gly  Ala Ser Ala Val Glu  Val
        1015                1020                1025

gcc gtg tcc ttc  agc cct gcc agg gac  ctg cct gac agc agc  ctg      3527
Ala Val Ser Phe  Ser Pro Ala Arg Asp  Leu Pro Asp Ser Ser  Leu
    1030                1035                1040

atc cag ggc gcg  gcc cac gcc atc gtg  gcc gcc atc acc cag  cgg      3572
Ile Gln Gly Ala  Ala His Ala Ile Val  Ala Ala Ile Thr Gln  Arg
1045                1050                1055

ggg aac agc tca  ctg ctc ctg gct gtc  acc gag gtc aag gtg  gag      3617
Gly Asn Ser Ser  Leu Leu Leu Ala Val  Thr Glu Val Lys Val  Glu
            1060                1065                1070

acg gtt gtt acg  ggc ggc tct tcc aca  ggt ctg ctg gtg cct  gtg      3662
Thr Val Val Thr  Gly Gly Ser Ser Thr  Gly Leu Leu Val Pro  Val
        1075                1080                1085

ctg tgt ggt gcc  ttc agc gtg ctg tgg  ctg gcg tgc gtg gtc  ctg      3707
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Leu Cys Gly Ala  Phe Ser Val Leu Trp  Leu Ala Cys Val Val  Leu
                1090                1095                1100

tgc gtg tgg tgg  aca cgc aag cgc agg  aaa gag cgg gag agg  agc      3752
Cys Val Trp Trp  Thr Arg Lys Arg Arg  Lys Glu Arg Glu Arg  Ser
                1105                1110                1115

cgg ctg ccg cgg  gag gag agc gcc aac  aac cag tgg gcc ccg  ctc      3797
Arg Leu Pro Arg  Glu Glu Ser Ala Asn  Asn Gln Trp Ala Pro  Leu
                1120                1125                1130

aac ccc atc cgc  aac ccc atc gag cgg  ccg ggg ggc cac aag  gac      3842
Asn Pro Ile Arg  Asn Pro Ile Glu Arg  Pro Gly Gly His Lys  Asp
                1135                1140                1145

gtg ctc tac cag  tgc aag aac ttc acg  ccg ccg ccg cgc agg  gcg      3887
Val Leu Tyr Gln  Cys Lys Asn Phe Thr  Pro Pro Pro Arg Arg  Ala
                1150                1155                1160

gac gag gcg ctg  ccc ggg ccg gcc ggc  cac gcg gcc gtc agg  gag      3932
Asp Glu Ala Leu  Pro Gly Pro Ala Gly  His Ala Ala Val Arg  Glu
                1165                1170                1175

gat gag gag gac  gag gat ctg ggc cgc  ggt gag gag gac tcc  ctg      3977
Asp Glu Glu Asp  Glu Asp Leu Gly Arg  Gly Glu Glu Asp Ser  Leu
                1180                1185                1190

gag gcg gag aag  ttc ctc tca cac aaa  ttc acc aaa gat cct  ggc      4022
Glu Ala Glu Lys  Phe Leu Ser His Lys  Phe Thr Lys Asp Pro  Gly
                1195                1200                1205

cgc tcg ccg ggg  agg ccg gcc cac tgg  gcc tca ggc ccc aaa  gtg      4067
Arg Ser Pro Gly  Arg Pro Ala His Trp  Ala Ser Gly Pro Lys  Val
                1210                1215                1220

gac aac cgc gcg  gtc agg agc atc aat  gag gcc cgc tac gcc  ggc      4112
Asp Asn Arg Ala  Val Arg Ser Ile Asn  Glu Ala Arg Tyr Ala  Gly
                1225                1230                1235

aag gag tag gggcggctgc cagctgggcc gggacccagg gccctcggtg           4161
Lys Glu

ggagccatgc cgtctgccgg acccggaggc cgaggccatg tgcatagttt ctttattttg  4221
tgtaaaaaaa ccaccaaaaa caaaaaccaa atgtttattt tctacgtttc tttaaccttg  4281
tataaattat tcagtaactg tcaggctgaa aacaatggag tattctcgga tagttgctat  4341
ttttgtaaag tttccgtgcg tggcactcgc tgtatgaaag gagagagcaa agggtgtctg  4401
cgtcgtcacc aaatcgtagc gtttgttacc agaggttgtg cactgtttac agaatcttcc  4461
ttttattcct cactcgggtt tctctgtggc tccaggccaa agtgccggtg agacccatgg  4521
ctgtgttggt gtggcccatg gctgttggtg ggacccgtgg ctgatggtgt ggcctgtggc  4581
tgtcggtggg actcgtggct gtcaatggga cctgtggctg tcggtgggac ctacggtggt  4641
cggtgggacc ctggttattg atgtggccct ggctgccggc acggcccgtg gctgttgacg  4701
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ccgctccagc gatctctcca ctgtgctttc agaagtgccc ttcctgctgc gcagttctcc  4881
catcctggga cggcggcagt attgaagctc gtgacaagtg ccttcacaca gacccctcgc  4941
aactgtccac gcgtgccgtg gcaccaggcg ctgcccacct gccggccccg gccgcccctc  5001
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ttgaataatg ccacca                                                  5077

<210>  38
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<212>  PRT
<213>  Homo sapiens
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Leu Ala Leu Trp Val Gln Ala Ala Arg Pro Met Gly Tyr Phe Glu Leu
20 25 30

Gln Leu Ser Ala Leu Arg Asn Val Asn Gly Glu Leu Leu Ser Gly Ala
35 40 45

Cys Cys Asp Gly Asp Gly Arg Thr Thr Arg Ala Gly Gly Cys Gly His
50 55 60

Asp Glu Cys Asp Thr Tyr Val Arg Val Cys Leu Lys Glu Tyr Gln Ala
65 70 75 80

Lys Val Thr Pro Thr Gly Pro Cys Ser Tyr Gly His Gly Ala Thr Pro
85 90 95

Val Leu Gly Gly Asn Ser Phe Tyr Leu Pro Pro Ala Gly Ala Ala Gly
100 105 110

Asp Arg Ala Arg Ala Arg Ala Arg Ala Gly Gly Asp Gln Asp Pro Gly
115 120 125

Leu Val Val Ile Pro Phe Gln Phe Ala Trp Pro Arg Ser Phe Thr Leu
130 135 140

Ile Val Glu Ala Trp Asp Trp Asp Asn Asp Thr Thr Pro Asn Glu Glu
145 150 155 160

Leu Leu Ile Glu Arg Val Ser His Ala Gly Met Ile Asn Pro Glu Asp
165 170 175

Arg Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu
180 185 190

Gln Ile Arg Val Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn
195 200 205

Lys Phe Cys Arg Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp
210 215 220

Gln Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys
225 230 235 240

Lys Glu Ala Val Cys Lys Gln Gly Cys Asn Leu Leu His Gly Gly Cys
245 250 255

Thr Val Pro Gly Glu Cys Arg Cys Ser Tyr Gly Trp Gln Gly Arg Phe
260 265 270

Cys Asp Glu Cys Val Pro Tyr Pro Gly Cys Val His Gly Ser Cys Val
275 280 285

Glu Pro Trp Gln Cys Asn Cys Glu Thr Asn Trp Gly Gly Leu Leu Cys
290 295 300

Asp Lys Asp Leu Asn Tyr Cys Gly Ser His His Pro Cys Thr Asn Gly
305 310 315 320

Gly Thr Cys Ile Asn Ala Glu Pro Asp Gln Tyr Arg Cys Thr Cys Pro
325 330 335

Asp Gly Tyr Ser Gly Arg Asn Cys Glu Lys Ala Glu His Ala Cys Thr
340 345 350

Ser Asn Pro Cys Ala Asn Gly Gly Ser Cys His Glu Val Pro Ser Gly
355 360 365

Phe Glu Cys His Cys Pro Ser Gly Trp Ser Gly Pro Thr Cys Ala Leu
370 375 380

Asp Ile Asp Glu Cys Ala Ser Asn Pro Cys Ala Ala Gly Gly Thr Cys
385 390 395 400

Val Asp Gln Val Asp Gly Phe Glu Cys Ile Cys Pro Glu Gln Trp Val
405 410 415

Gly Ala Thr Cys Gln Leu Asp Ala Asn Glu Cys Glu Gly Lys Pro Cys
420 425 430

Leu Asn Ala Phe Ser Cys Lys Asn Leu Ile Gly Gly Tyr Tyr Cys Asp
435 440 445

Cys Ile Pro Gly Trp Lys Gly Ile Asn Cys His Ile Asn Val Asn Asp
450 455 460

Cys Arg Gly Gln Cys Gln His Gly Gly Thr Cys Lys Asp Leu Val Asn
465 470 475 480

Gly Tyr Gln Cys Val Cys Pro Arg Gly Phe Gly Gly Arg His Cys Glu
485 490 495

Leu Glu Arg Asp Glu Cys Ala Ser Ser Pro Cys His Ser Gly Gly Leu
500 505 510

Cys Glu Asp Leu Ala Asp Gly Phe His Cys His Cys Pro Gln Gly Phe
515 520 525

Ser Gly Pro Leu Cys Glu Val Asp Val Asp Leu Cys Glu Pro Ser Pro
530 535 540

Cys Arg Asn Gly Ala Arg Cys Tyr Asn Leu Glu Gly Asp Tyr Tyr Cys
545 550 555 560

Ala Cys Pro Asp Asp Phe Gly Gly Lys Asn Cys Ser Val Pro Arg Glu
565 570 575

Pro Cys Pro Gly Gly Ala Cys Arg Val Ile Asp Gly Cys Gly Ser Asp
580 585 590

Ala Gly Pro Gly Met Pro Gly Thr Ala Ala Ser Gly Val Cys Gly Pro
595 600 605

His Gly Arg Cys Val Ser Gln Pro Gly Gly Asn Phe Ser Cys Ile Cys
610 615 620

Asp Ser Gly Phe Thr Gly Thr Tyr Cys His Glu Asn Ile Asp Asp Cys
625 630 635 640

Leu Gly Gln Pro Cys Arg Asn Gly Gly Thr Cys Ile Asp Glu Val Asp
645 650 655

Ala Phe Arg Cys Phe Cys Pro Ser Gly Trp Glu Gly Glu Leu Cys Asp
660 665 670

Thr Asn Pro Asn Asp Cys Leu Pro Asp Pro Cys His Ser Arg Gly Arg
675 680 685

Cys Tyr Asp Leu Val Asn Asp Phe Tyr Cys Ala Cys Asp Asp Gly Trp
690 695 700

Lys Gly Lys Thr Cys His Ser Arg Glu Phe Gln Cys Asp Ala Tyr Thr
705 710 715 720

Cys Ser Asn Gly Gly Thr Cys Tyr Asp Ser Gly Asp Thr Phe Arg Cys
725 730 735

Ala Cys Pro Pro Gly Trp Lys Gly Ser Thr Cys Ala Val Ala Lys Asn
740 745 750

Ser Ser Cys Leu Pro Asn Pro Cys Val Asn Gly Gly Thr Cys Val Gly
755 760 765

Ser Gly Ala Ser Phe Ser Cys Ile Cys Arg Asp Gly Trp Glu Gly Arg
770 775 780

Thr Cys Thr His Asn Thr Asn Asp Cys Asn Pro Leu Pro Cys Tyr Asn
785 790 795 800

Gly Gly Ile Cys Val Asp Gly Val Asn Trp Phe Arg Cys Glu Cys Ala
805 810 815

Pro Gly Phe Ala Gly Pro Asp Cys Arg Ile Asn Ile Asp Glu Cys Gln
820 825 830

Ser Ser Pro Cys Ala Tyr Gly Ala Thr Cys Val Asp Glu Ile Asn Gly
835 840 845

Tyr Arg Cys Ser Cys Pro Pro Gly Arg Ala Gly Pro Arg Cys Gln Glu
850 855 860

Val Ile Gly Phe Gly Arg Ser Cys Trp Ser Arg Gly Thr Pro Phe Pro
865 870 875 880

His Gly Ser Ser Trp Val Glu Asp Cys Asn Ser Cys Arg Cys Leu Asp
885 890 895

Gly Arg Arg Asp Cys Ser Lys Val Trp Cys Gly Trp Lys Pro Cys Leu
900 905 910

Leu Ala Gly Gln Pro Glu Ala Leu Ser Ala Gln Cys Pro Leu Gly Gln
915 920 925

Arg Cys Leu Glu Lys Ala Pro Gly Gln Cys Leu Arg Pro Pro Cys Glu
930 935 940

Ala Trp Gly Glu Cys Gly Ala Glu Glu Pro Pro Ser Thr Pro Cys Leu
945 950 955 960

Pro Arg Ser Gly His Leu Asp Asn Asn Cys Ala Arg Leu Thr Leu His
965 970 975

Phe Asn Arg Asp His Val Pro Gln Gly Thr Thr Val Gly Ala Ile Cys
980 985 990

Ser Gly Ile Arg Ser Leu Pro Ala Thr Arg Ala Val Ala Arg Asp Arg
995 1000 1005

Leu Leu Val Leu Leu Cys Asp Arg Ala Ser Ser Gly Ala Ser Ala
1010 1015 1020

Val Glu Val Ala Val Ser Phe Ser Pro Ala Arg Asp Leu Pro Asp
1025 1030 1035

Ser Ser Leu Ile Gln Gly Ala Ala His Ala Ile Val Ala Ala Ile
1040 1045 1050

Thr Gln Arg Gly Asn Ser Ser Leu Leu Leu Ala Val Thr Glu Val
1055 1060 1065

Lys Val Glu Thr Val Val Thr Gly Gly Ser Ser Thr Gly Leu Leu
1070 1075 1080

Val Pro Val Leu Cys Gly Ala Phe Ser Val Leu Trp Leu Ala Cys
1085 1090 1095

Val Val Leu Cys Val Trp Trp Thr Arg Lys Arg Arg Lys Glu Arg
1100 1105 1110

Glu Arg Ser Arg Leu Pro Arg Glu Glu Ser Ala Asn Asn Gln Trp
1115 1120 1125

Ala Pro Leu Asn Pro Ile Arg Asn Pro Ile Glu Arg Pro Gly Gly
1130 1135 1140

His Lys Asp Val Leu Tyr Gln Cys Lys Asn Phe Thr Pro Pro Pro
1145 1150 1155

Arg Arg Ala Asp Glu Ala Leu Pro Gly Pro Ala Gly His Ala Ala
1160 1165 1170

Val Arg Glu Asp Glu Glu Asp Glu Asp Leu Gly Arg Gly Glu Glu
1175 1180 1185

Asp Ser Leu Glu Ala Glu Lys Phe Leu Ser His Lys Phe Thr Lys
1190 1195 1200

Asp Pro Gly Arg Ser Pro Gly Arg Pro Ala His Trp Ala Ser Gly
1205 1210 1215

Pro Lys Val Asp Asn Arg Ala Val Arg Ser Ile Asn Glu Ala Arg
1220 1225 1230

Tyr Ala Gly Lys Glu
1235

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<212> DNA
<213> Homo sapiens

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<222> (3)..(371)
<223>

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Arg Ala Ala Leu Arg Arg Leu Ala Val Ala Thr Arg Thr Met Ala
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gga gcg ccc acg gtc tcg ctt cct gaa ctc cgt tca ctc cta gcc tcc 95
Gly Ala Pro Thr Val Ser Leu Pro Glu Leu Arg Ser Leu Leu Ala Ser
20 25 30

gga cgg gcc cgg ctc ttc gac gtg cgc tct cgc gag gag gcg gca gct 143
Gly Arg Ala Arg Leu Phe Asp Val Arg Ser Arg Glu Glu Ala Ala Ala
35 40 45

ggg acc atc cca ggg gcg ctc aac atc ccg gtg tcc gag ttg gag agt 191
Gly Thr Ile Pro Gly Ala Leu Asn Ile Pro Val Ser Glu Leu Glu Ser
50 55 60

gct ctg cag atg gag cca gct gcc ttc cag gct tta tat tct gct gag 239
Ala Leu Gln Met Glu Pro Ala Ala Phe Gln Ala Leu Tyr Ser Ala Glu
65 70 75

aag cca aag ctg gaa gat gag cat ctc gtt ttc ttc tgt cag atg ggc 287
Lys Pro Lys Leu Glu Asp Glu His Leu Val Phe Phe Cys Gln Met Gly
80 85 90 95

aag cgg ggc ctc cag gcc acg cag ctg gcc cgg agt ctt gga tac act 335
Lys Arg Gly Leu Gln Ala Thr Gln Leu Ala Arg Ser Leu Gly Tyr Thr
100 105 110

ggg tac ggg gag gtg tgg ctg cta gct ggg agg tga tggggactgc 381
Gly Tyr Gly Glu Val Trp Leu Leu Ala Gly Arg
115 120

ctgtcattcc tgtcagtctc tcacgcttct ttgtctccac agggctcgca actacgctgg 441

agcctataga gaatggttgg agaaagagag ttaggcagga ggcagcttac tgattgccac 501

cccctggccc cttaatggcc accttaacta agggtgtgaa cgggctgact tggtgaattg 561

ggcaactcct tatagtgttg tgcacacaaa agcatcaaat aaagaacatt taatcaaaaa 621

aaaaaaaaaa aaa 634

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<212> PRT
<213> Homo sapiens

<400> 40

Arg Ala Ala Leu Arg Arg Leu Ala Val Ala Thr Arg Thr Met Ala Gly
1 5 10 15

Ala Pro Thr Val Ser Leu Pro Glu Leu Arg Ser Leu Leu Ala Ser Gly
20 25 30

Arg Ala Arg Leu Phe Asp Val Arg Ser Arg Glu Glu Ala Ala Ala Gly
35 40 45

Thr Ile Pro Gly Ala Leu Asn Ile Pro Val Ser Glu Leu Glu Ser Ala
50 55 60

Leu Gln Met Glu Pro Ala Ala Phe Gln Ala Leu Tyr Ser Ala Glu Lys
65 70 75 80

Pro Lys Leu Glu Asp Glu His Leu Val Phe Phe Cys Gln Met Gly Lys
85 90 95

Arg Gly Leu Gln Ala Thr Gln Leu Ala Arg Ser Leu Gly Tyr Thr Gly
100 105 110

Tyr Gly Glu Val Trp Leu Leu Ala Gly Arg
115 120

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<223>

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tgggagaggc ttctgggtca aaggaccagt ctgcagaggg atcctgtggc tggaagcgag 120

gaggctccac acggccgttg cagctaccgc agccaggatc tgggcatcca ggcacggcc 179

atg acc cct ccg agg ctc ttc tgg gtg tgg ctg ctg gtt gca gga acc 227
Met Thr Pro Pro Arg Leu Phe Trp Val Trp Leu Leu Val Ala Gly Thr
1 5 10 15

caa ggc gtg aac gat ggt gac atg cgg ctg gcc gat ggg ggc gcc acc 275
Gln Gly Val Asn Asp Gly Asp Met Arg Leu Ala Asp Gly Gly Ala Thr
20 25 30

aac cag ggc cgc gtg gag atc ttc tac aga ggc cag tgg ggc act gtg 323
Asn Gln Gly Arg Val Glu Ile Phe Tyr Arg Gly Gln Trp Gly Thr Val
35 40 45

tgt gac aac ctg tgg gac ctg act gat gcc agc gtc gtc tgc cgg gcc 371
Cys Asp Asn Leu Trp Asp Leu Thr Asp Ala Ser Val Val Cys Arg Ala
50 55 60

ctg ggc ttc gag aac gcc acc cag gct ctg ggc aga gct gcc ttc ggg 419
Leu Gly Phe Glu Asn Ala Thr Gln Ala Leu Gly Arg Ala Ala Phe Gly
65 70 75 80

caa gga tca ggc ccc atc atg ctg gac gag gtc cag tgc acg gga acc 467
Gln Gly Ser Gly Pro Ile Met Leu Asp Glu Val Gln Cys Thr Gly Thr
85 90 95

gag gcc tca ctg gcc gac tgc aag tcc ctg ggc tgg ctg aag agc aac 515
Glu Ala Ser Leu Ala Asp Cys Lys Ser Leu Gly Trp Leu Lys Ser Asn
100 105 110

tgc agg cac gag aga gac gct ggt gtg gtc tgc acc aat gaa acc agg 563
Cys Arg His Glu Arg Asp Ala Gly Val Val Cys Thr Asn Glu Thr Arg
115 120 125

agc acc cac acc ctg gac ctc tcc agg gag ctc tcg gag gcc ctt ggc 611
Ser Thr His Thr Leu Asp Leu Ser Arg Glu Leu Ser Glu Ala Leu Gly
130 135 140

cag atc ttt gac agc cag cgg ggc tgc gac ctg tcc atc agc gtg aat 659
Gln Ile Phe Asp Ser Gln Arg Gly Cys Asp Leu Ser Ile Ser Val Asn
145 150 155 160

gtg cag ggc gag gac gcc ctg ggc ttc tgt ggc cac acg gtc atc ctg 707
Val Gln Gly Glu Asp Ala Leu Gly Phe Cys Gly His Thr Val Ile Leu
165 170 175

act gcc aac ctg gag gcc cag gcc ctg tgg aag gag ccg ggc agc aat 755
Thr Ala Asn Leu Glu Ala Gln Ala Leu Trp Lys Glu Pro Gly Ser Asn
180 185 190

gtc acc atg agt gtg gat gct gag tgt gtg ccc atg gtc agg gac ctt 803
Val Thr Met Ser Val Asp Ala Glu Cys Val Pro Met Val Arg Asp Leu
195 200 205

ctc agg tac ttc tac tcc cga agg att gac atc acc ctg tcg tca gtc 851
Leu Arg Tyr Phe Tyr Ser Arg Arg Ile Asp Ile Thr Leu Ser Ser Val
210 215 220

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aag tgc ttc cac aag ctg gcc tct gcc tat ggg gcc agg cag ctg cag      899
Lys Cys Phe His Lys Leu Ala Ser Ala Tyr Gly Ala Arg Gln Leu Gln
225                 230                 235                 240

ggc tac tgc gca agc ctc ttt gcc atc ctc ctc ccc cag gac ccc tcg      947
Gly Tyr Cys Ala Ser Leu Phe Ala Ile Leu Leu Pro Gln Asp Pro Ser
                245                 250                 255

ttc cag atg ccc ctg gac ctg tat gcc tat gca gtg gcc aca ggg gac      995
Phe Gln Met Pro Leu Asp Leu Tyr Ala Tyr Ala Val Ala Thr Gly Asp
            260                 265                 270

gcc ctg ctg gag aag ctc tgc cta cag ttc ctg gcc tgg aac ttc gag     1043
Ala Leu Leu Glu Lys Leu Cys Leu Gln Phe Leu Ala Trp Asn Phe Glu
        275                 280                 285

gcc ttg acg cag gcc gag gcc tgg ccc agt gtc ccc aca gac ctg ctc     1091
Ala Leu Thr Gln Ala Glu Ala Trp Pro Ser Val Pro Thr Asp Leu Leu
    290                 295                 300

caa ctg ctg ctg ccc agg agc gac ctg gcg gtg ccc agc gag ctg gcc     1139
Gln Leu Leu Leu Pro Arg Ser Asp Leu Ala Val Pro Ser Glu Leu Ala
305                 310                 315                 320

cta ctg aag gcc gtg gac acc tgg agc tgg ggg gag cgt gcc tcc cat     1187
Leu Leu Lys Ala Val Asp Thr Trp Ser Trp Gly Glu Arg Ala Ser His
                325                 330                 335

gag gag gtg gag ggc ttg gtg gag aag atc cgc ttc ccc atg atg ctc     1235
Glu Glu Val Glu Gly Leu Val Glu Lys Ile Arg Phe Pro Met Met Leu
            340                 345                 350

cct gag gag ctc ttt gag ctg cag ttc aac ctg tcc ctg tac tgg agc     1283
Pro Glu Glu Leu Phe Glu Leu Gln Phe Asn Leu Ser Leu Tyr Trp Ser
        355                 360                 365

cac gag gcc ctg ttc cag aag aag act ctg cag gcc ctg gaa ttc cac     1331
His Glu Ala Leu Phe Gln Lys Lys Thr Leu Gln Ala Leu Glu Phe His
    370                 375                 380

act gtg ccc ttc cag ttg ctg gcc cgg tac aaa ggc ctg aac ctc acc     1379
Thr Val Pro Phe Gln Leu Leu Ala Arg Tyr Lys Gly Leu Asn Leu Thr
385                 390                 395                 400

gag gat acc tac aag ccc cgg att tac acc tcg ccc acc tgg agt gcc     1427
Glu Asp Thr Tyr Lys Pro Arg Ile Tyr Thr Ser Pro Thr Trp Ser Ala
                405                 410                 415

ttt gtg aca gac agt tcc tgg agt gca cgg aag tca caa ctg gtc tat     1475
Phe Val Thr Asp Ser Ser Trp Ser Ala Arg Lys Ser Gln Leu Val Tyr
            420                 425                 430

cag tcc aga cgg ggg cct ttg gtc aaa tat tct tct gat tac ttc caa     1523
Gln Ser Arg Arg Gly Pro Leu Val Lys Tyr Ser Ser Asp Tyr Phe Gln
        435                 440                 445

gcc ccc tct gac tac aga tac tac ccc tac cag tcc ttc cag act cca     1571
Ala Pro Ser Asp Tyr Arg Tyr Tyr Pro Tyr Gln Ser Phe Gln Thr Pro
    450                 455                 460

caa cac ccc agc ttc ctc ttc cag gac aag agg gtg tcc tgg tcc ctg     1619
Gln His Pro Ser Phe Leu Phe Gln Asp Lys Arg Val Ser Trp Ser Leu
465                 470                 475                 480

gtc tac ctc ccc acc atc cag agc tgc tgg aac tac ggc ttc tcc tgc     1667
Val Tyr Leu Pro Thr Ile Gln Ser Cys Trp Asn Tyr Gly Phe Ser Cys
                485                 490                 495

tcc tcg gac gag ctc cct gtc ctg ggc ctc acc aag tct ggc ggc tca     1715
Ser Ser Asp Glu Leu Pro Val Leu Gly Leu Thr Lys Ser Gly Gly Ser
            500                 505                 510

gat cgc acc att gcc tac gaa aac aaa gcc ctg atg ctc tgc gaa ggg     1763
Asp Arg Thr Ile Ala Tyr Glu Asn Lys Ala Leu Met Leu Cys Glu Gly
        515                 520                 525

ctc ttc gtg gca gac gtc acc gat ttc gag ggc tgg aag gct gcg att     1811
Leu Phe Val Ala Asp Val Thr Asp Phe Glu Gly Trp Lys Ala Ala Ile
    530                 535                 540
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ccc agt gcc ctg gac acc aac agc tcg aag agc acc tcc tcc ttc ccc 1859
Pro Ser Ala Leu Asp Thr Asn Ser Ser Lys Ser Thr Ser Ser Phe Pro
545 550 555 560

tgc ccg gca ggg cac ttc aac ggc ttc cgc acg gtc atc cgc ccc ttc 1907
Cys Pro Ala Gly His Phe Asn Gly Phe Arg Thr Val Ile Arg Pro Phe
565 570 575

tac ctg acc aac tcc tca ggt gtg gac tag acgcgtggcc aagggtggtg 1957
Tyr Leu Thr Asn Ser Ser Gly Val Asp
580 585

agaaccggag aaccccagga cgccctcact gcaggctccc ctcctcggct tccttcctct 2017

ctgcaatgac cttcaacaac cggccaccag atgtcgccct actcacctga ggctcagctt 2077

caagaaatta ctggaaggct tccactaggg tccaccagga gttctcccac cacctcacca 2137

gtttccaggt ggtaagcacc aggaggccct cgaggttgct ctggatcccc ccacagcccc 2197

tggtcagtct gcccttgtca ctggtctgag gtcattaaaa ttacattgag gttccta 2254

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<212> PRT
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<400> 42

Met Thr Pro Pro Arg Leu Phe Trp Val Trp Leu Leu Val Ala Gly Thr
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Gln Gly Val Asn Asp Gly Asp Met Arg Leu Ala Asp Gly Gly Ala Thr
20 25 30

Asn Gln Gly Arg Val Glu Ile Phe Tyr Arg Gly Gln Trp Gly Thr Val
35 40 45

Cys Asp Asn Leu Trp Asp Leu Thr Asp Ala Ser Val Val Cys Arg Ala
50 55 60

Leu Gly Phe Glu Asn Ala Thr Gln Ala Leu Gly Arg Ala Ala Phe Gly
65 70 75 80

Gln Gly Ser Gly Pro Ile Met Leu Asp Glu Val Gln Cys Thr Gly Thr
85 90 95

Glu Ala Ser Leu Ala Asp Cys Lys Ser Leu Gly Trp Leu Lys Ser Asn
100 105 110

Cys Arg His Glu Arg Asp Ala Gly Val Val Cys Thr Asn Glu Thr Arg
115 120 125

Ser Thr His Thr Leu Asp Leu Ser Arg Glu Leu Ser Glu Ala Leu Gly
130 135 140

Gln Ile Phe Asp Ser Gln Arg Gly Cys Asp Leu Ser Ile Ser Val Asn
145 150 155 160

Val Gln Gly Glu Asp Ala Leu Gly Phe Cys Gly His Thr Val Ile Leu
165 170 175

Thr Ala Asn Leu Glu Ala Gln Ala Leu Trp Lys Glu Pro Gly Ser Asn
180 185 190

Val Thr Met Ser Val Asp Ala Glu Cys Val Pro Met Val Arg Asp Leu
195 200 205

Leu Arg Tyr Phe Tyr Ser Arg Arg Ile Asp Ile Thr Leu Ser Ser Val
210 215 220

Lys Cys Phe His Lys Leu Ala Ser Ala Tyr Gly Ala Arg Gln Leu Gln
225 230 235 240

Gly Tyr Cys Ala Ser Leu Phe Ala Ile Leu Leu Pro Gln Asp Pro Ser
245 250 255

Phe Gln Met Pro Leu Asp Leu Tyr Ala Tyr Ala Val Ala Thr Gly Asp
260 265 270

Ala Leu Leu Glu Lys Leu Cys Leu Gln Phe Leu Ala Trp Asn Phe Glu
275 280 285

Ala Leu Thr Gln Ala Glu Ala Trp Pro Ser Val Pro Thr Asp Leu Leu
290 295 300

Gln Leu Leu Leu Pro Arg Ser Asp Leu Ala Val Pro Ser Glu Leu Ala
305 310 315 320

Leu Leu Lys Ala Val Asp Thr Trp Ser Trp Gly Glu Arg Ala Ser His
325 330 335

Glu Glu Val Glu Gly Leu Val Glu Lys Ile Arg Phe Pro Met Met Leu
340 345 350

Pro Glu Glu Leu Phe Glu Leu Gln Phe Asn Leu Ser Leu Tyr Trp Ser
355 360 365

His Glu Ala Leu Phe Gln Lys Lys Thr Leu Gln Ala Leu Glu Phe His
370 375 380

Thr Val Pro Phe Gln Leu Leu Ala Arg Tyr Lys Gly Leu Asn Leu Thr
385 390 395 400

Glu Asp Thr Tyr Lys Pro Arg Ile Tyr Thr Ser Pro Thr Trp Ser Ala
405 410 415

Phe Val Thr Asp Ser Ser Trp Ser Ala Arg Lys Ser Gln Leu Val Tyr
420 425 430

Gln Ser Arg Arg Gly Pro Leu Val Lys Tyr Ser Ser Asp Tyr Phe Gln
435 440 445

Ala Pro Ser Asp Tyr Arg Tyr Tyr Pro Tyr Gln Ser Phe Gln Thr Pro
450 455 460

Gln His Pro Ser Phe Leu Phe Gln Asp Lys Arg Val Ser Trp Ser Leu
465 470 475 480

Val Tyr Leu Pro Thr Ile Gln Ser Cys Trp Asn Tyr Gly Phe Ser Cys
485 490 495

Ser Ser Asp Glu Leu Pro Val Leu Gly Leu Thr Lys Ser Gly Gly Ser
500 505 510

Asp Arg Thr Ile Ala Tyr Glu Asn Lys Ala Leu Met Leu Cys Glu Gly
515 520 525

Leu Phe Val Ala Asp Val Thr Asp Phe Glu Gly Trp Lys Ala Ala Ile
530 535 540

Pro Ser Ala Leu Asp Thr Asn Ser Ser Lys Ser Thr Ser Ser Phe Pro
545 550 555 560

Cys Pro Ala Gly His Phe Asn Gly Phe Arg Thr Val Ile Arg Pro Phe
565 570 575

Tyr Leu Thr Asn Ser Ser Gly Val Asp
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aaggagctct acaacgtgct gcctggtggc gagaaggagt tcgtgaacct gcagggtttt 180

gccgccagag gcttcgaggg cttctgcctg gttggcgtct ccgacctgga catctgtgag 240

ttcattgaca actatgcgct ctccaagaag ggtgtcaaag cc atg agc ctc aag 294
Met Ser Leu Lys
1

cgc tcc acc atc acg gac gca ggc ctc gag gtt atg ctt gaa cag atg 342
Arg Ser Thr Ile Thr Asp Ala Gly Leu Glu Val Met Leu Glu Gln Met
5 10 15 20

cag ggc gtg gtg cgt ctg gag ctg tcg ggc tgc aac gac ttc acc gag 390
Gln Gly Val Val Arg Leu Glu Leu Ser Gly Cys Asn Asp Phe Thr Glu
25 30 35

gcc ggg ctg tgg tcc agc ctg agc gcg cgc atc acc tcg ctg agc gtg 438
Ala Gly Leu Trp Ser Ser Leu Ser Ala Arg Ile Thr Ser Leu Ser Val
40 45 50

agt gac tgc atc aac gtg gcc gac gac gcc atc gcg gcc atc tcg cag 486
Ser Asp Cys Ile Asn Val Ala Asp Asp Ala Ile Ala Ala Ile Ser Gln
55 60 65

ctg ctg ccc aac ctg gcg gag ctg agc ctg cag gcc tac cac gtg acg 534
Leu Leu Pro Asn Leu Ala Glu Leu Ser Leu Gln Ala Tyr His Val Thr
70 75 80

gac acg gcg ctg gcc tac ttc acg gcg cgc cag ggc cac agc acg cac 582
Asp Thr Ala Leu Ala Tyr Phe Thr Ala Arg Gln Gly His Ser Thr His
85 90 95 100

acg ctg cgc ctg ctc tcc tgc tgg gag atc acc aac cac ggc gtg gtc 630
Thr Leu Arg Leu Leu Ser Cys Trp Glu Ile Thr Asn His Gly Val Val
105 110 115

aac gtg gtg cac agc ctg ccc aac ctc acc gcg ctc agc ctc tcg ggc 678
Asn Val Val His Ser Leu Pro Asn Leu Thr Ala Leu Ser Leu Ser Gly
120 125 130

tgc tcc aag gtc acc gac gac ggc gtg gag ctc gtg gcc gag aac ctg 726
Cys Ser Lys Val Thr Asp Asp Gly Val Glu Leu Val Ala Glu Asn Leu
135 140 145

cgc aag ctg cgc agc ctt gac ctc tcg tgg tgc cca cgc atc acc gac 774
Arg Lys Leu Arg Ser Leu Asp Leu Ser Trp Cys Pro Arg Ile Thr Asp
150 155 160

atg gcg ctg gag tac gtg gcc tgc gac ctg cac cgc cta gag gag ctc 822

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Met Ala Leu Glu Tyr Val Ala Cys Asp Leu His Arg Leu Glu Glu Leu
165                 170                 175                 180

gtg ctc gac agg tgt gta cgc atc acg gac act ggc ctc agc tat ctg      870
Val Leu Asp Arg Cys Val Arg Ile Thr Asp Thr Gly Leu Ser Tyr Leu
                185                 190                 195

tcc acc atg tcg tcc ctc cgc agc ctc tac ctg cga tgg tgc tgc cag      918
Ser Thr Met Ser Ser Leu Arg Ser Leu Tyr Leu Arg Trp Cys Cys Gln
            200                 205                 210

gtg caa gac ttc ggg ctg aag cac ctc ctg gcc ctg ggg agt ttg cgc      966
Val Gln Asp Phe Gly Leu Lys His Leu Leu Ala Leu Gly Ser Leu Arg
        215                 220                 225

ctc ctg tct ctg gca ggc tgc ccg ctg ctc acc acc acc ggg ctg tcg     1014
Leu Leu Ser Leu Ala Gly Cys Pro Leu Leu Thr Thr Thr Gly Leu Ser
    230                 235                 240

ggc ctg gtg cag ctg cag gag ctg gag gag ctg gag ctg acc aac tgc     1062
Gly Leu Val Gln Leu Gln Glu Leu Glu Glu Leu Glu Leu Thr Asn Cys
245                 250                 255                 260

ccc ggg gcc acc ccc gag ctc ttc aag tat ttc tcg cag cac ctg ccc     1110
Pro Gly Ala Thr Pro Glu Leu Phe Lys Tyr Phe Ser Gln His Leu Pro
                265                 270                 275

cgc tgc ctc gtc att gag tag cgcgaggccc ccgccccggt cgcgggaacc        1161
Arg Cys Leu Val Ile Glu
            280

cggccatgac ctgggcgggg gcgc                                         1185

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<212>  PRT
<213>  Homo sapiens

<400>  44

Met Ser Leu Lys Arg Ser Thr Ile Thr Asp Ala Gly Leu Glu Val Met
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Leu Glu Gln Met Gln Gly Val Val Arg Leu Glu Leu Ser Gly Cys Asn
            20                  25                  30

Asp Phe Thr Glu Ala Gly Leu Trp Ser Ser Leu Ser Ala Arg Ile Thr
        35                  40                  45

Ser Leu Ser Val Ser Asp Cys Ile Asn Val Ala Asp Asp Ala Ile Ala
    50                  55                  60

Ala Ile Ser Gln Leu Leu Pro Asn Leu Ala Glu Leu Ser Leu Gln Ala
65                  70                  75                  80

Tyr His Val Thr Asp Thr Ala Leu Ala Tyr Phe Thr Ala Arg Gln Gly
                85                  90                  95

His Ser Thr His Thr Leu Arg Leu Leu Ser Cys Trp Glu Ile Thr Asn
            100                 105                 110

His Gly Val Val Asn Val Val His Ser Leu Pro Asn Leu Thr Ala Leu
        115                 120                 125

Ser Leu Ser Gly Cys Ser Lys Val Thr Asp Asp Gly Val Glu Leu Val
    130                 135                 140

Ala Glu Asn Leu Arg Lys Leu Arg Ser Leu Asp Leu Ser Trp Cys Pro
145                 150                 155                 160
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Arg Ile Thr Asp Met Ala Leu Glu Tyr Val Ala Cys Asp Leu His Arg
165 170 175

Leu Glu Glu Leu Val Leu Asp Arg Cys Val Arg Ile Thr Asp Thr Gly
180 185 190

Leu Ser Tyr Leu Ser Thr Met Ser Ser Leu Arg Ser Leu Tyr Leu Arg
195 200 205

Trp Cys Cys Gln Val Gln Asp Phe Gly Leu Lys His Leu Leu Ala Leu
210 215 220

Gly Ser Leu Arg Leu Leu Ser Leu Ala Gly Cys Pro Leu Leu Thr Thr
225 230 235 240

Thr Gly Leu Ser Gly Leu Val Gln Leu Gln Glu Leu Glu Glu Leu Glu
245 250 255

Leu Thr Asn Cys Pro Gly Ala Thr Pro Glu Leu Phe Lys Tyr Phe Ser
260 265 270

Gln His Leu Pro Arg Cys Leu Val Ile Glu
275 280

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ccagctggcg cgcccctccc atttgcctgt cctggtcagg cccccacccc ccttcccacc 180

tgaccagcc atg ggg gct gcg gtg ttt ttc ggc tgc act ttc gtc gcg ttc 231
Met Gly Ala Ala Val Phe Phe Gly Cys Thr Phe Val Ala Phe
1 5 10

ggc ccg gcc ttc gcg ctt ttc ttg atc act gtg gct ggg gac ccg ctt 279
Gly Pro Ala Phe Ala Leu Phe Leu Ile Thr Val Ala Gly Asp Pro Leu
15 20 25 30

cgc gtt atc atc ctg gtc gca ggg gca ttt ttc tgg ctg gtc tcc ctg 327
Arg Val Ile Ile Leu Val Ala Gly Ala Phe Phe Trp Leu Val Ser Leu
35 40 45

ctc ctg gcc tct gtg gtc tgg ttc atc ttg gtc cat gtg acc gac cgg 375
Leu Leu Ala Ser Val Val Trp Phe Ile Leu Val His Val Thr Asp Arg
50 55 60

tca gat gcc cgg ctc cag tac ggc ctc ctg att ttt ggt gct gct gtc 423
Ser Asp Ala Arg Leu Gln Tyr Gly Leu Leu Ile Phe Gly Ala Ala Val
65 70 75

tct gtc ctt cta cag gag gtg ttc cgc ttt gcc tac tac aag ctg ctt 471
Ser Val Leu Leu Gln Glu Val Phe Arg Phe Ala Tyr Tyr Lys Leu Leu
80 85 90

aag aag gca gat gag ggg tta gca tcg ctg agt gag gac gga aga tca 519
Lys Lys Ala Asp Glu Gly Leu Ala Ser Leu Ser Glu Asp Gly Arg Ser
95 100 105 110

ccc atc tcc atc cgc cag atg gcc tat gtt tct ggt ctc tcc ttc ggt 567
Pro Ile Ser Ile Arg Gln Met Ala Tyr Val Ser Gly Leu Ser Phe Gly
115 120 125

atc atc agt ggt gtc ttc tct gtt atc aat att ttg gct gat gca ctt 615
Ile Ile Ser Gly Val Phe Ser Val Ile Asn Ile Leu Ala Asp Ala Leu
130 135 140

ggg cca ggt gtg gtt ggg atc cat gga gac tca ccc tat tac ttc ctg 663
Gly Pro Gly Val Val Gly Ile His Gly Asp Ser Pro Tyr Tyr Phe Leu
145 150 155

act tca gcc ttt ctg aca gca gcc att atc ctg ctc cat acc ttt tgg 711
Thr Ser Ala Phe Leu Thr Ala Ala Ile Ile Leu Leu His Thr Phe Trp
160 165 170

gga gtt gtg ttc ttt gat gcc tgt gag agg aga cgg tac tgg gct ttg 759
Gly Val Val Phe Phe Asp Ala Cys Glu Arg Arg Arg Tyr Trp Ala Leu
175 180 185 190

ggc ctg gtg gtt ggg agt cac cta ctg aca tcg gga ctg aca ttc ctg 807
Gly Leu Val Val Gly Ser His Leu Leu Thr Ser Gly Leu Thr Phe Leu
195 200 205

aac ccc tgg tat gag gcc agc ctg ctg ccc atc tat gca gtc act gtt 855
Asn Pro Trp Tyr Glu Ala Ser Leu Leu Pro Ile Tyr Ala Val Thr Val
210 215 220

tcc atg ggg ctc tgg gcc ttc atc aca gct gga ggg tcc ctc cga agt 903
Ser Met Gly Leu Trp Ala Phe Ile Thr Ala Gly Gly Ser Leu Arg Ser
225 230 235

att cag cgc agc ctc ttg tgc cga cgg cag gag gac agt cgg gtg atg 951
Ile Gln Arg Ser Leu Leu Cys Arg Arg Gln Glu Asp Ser Arg Val Met
240 245 250

gtg tat tct gcc ctg cgc atc cca ccc gag gac tga gggaacctag 997
Val Tyr Ser Ala Leu Arg Ile Pro Pro Glu Asp
255 260 265

gggggacccc tgggcctggg gtgccctcct gatgtcctcg ccctgtattt ctccatctcc 1057

agttctggac agtgcaggtt gccaagaaaa gggacctagt ttagccattg ccctggagat 1117

gaaattaatg gaggctcaag gatagatgag ctctgagttt ctcagtactc cctcaagact 1177

ggacatcttg gtctttttct caggcctgag ggggaaccat ttttggtgtg ataaataccc 1237

taaactgcct ttttttcttt tttgaggtgg ggggagggag gaggtatatt ggaactcttc 1297

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ggcattactg gaactaatgg ttttaacctc cttaaccacc agcatccctc ctctccccaa 1477

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gtcagactac catgacatcg tagggaagga ggggagattt ttttgtagtt tttaattggg 1597

gtgtgggagg ggcggggagg ttttctataa actgtatcat tttctgctga gggtggagtg 1657

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1777

aaa 1780

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<211> 265
<212> PRT
<213> Homo sapiens

<400> 46

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Ala Phe Ala Leu Phe Leu Ile Thr Val Ala Gly Asp Pro Leu Arg Val
20 25 30

Ile Ile Leu Val Ala Gly Ala Phe Phe Trp Leu Val Ser Leu Leu Leu
35 40 45

Ala Ser Val Val Trp Phe Ile Leu Val His Val Thr Asp Arg Ser Asp
50 55 60

Ala Arg Leu Gln Tyr Gly Leu Leu Ile Phe Gly Ala Ala Val Ser Val
65 70 75 80

Leu Leu Gln Glu Val Phe Arg Phe Ala Tyr Tyr Lys Leu Leu Lys Lys
85 90 95

Ala Asp Glu Gly Leu Ala Ser Leu Ser Glu Asp Gly Arg Ser Pro Ile
100 105 110

Ser Ile Arg Gln Met Ala Tyr Val Ser Gly Leu Ser Phe Gly Ile Ile
115 120 125

Ser Gly Val Phe Ser Val Ile Asn Ile Leu Ala Asp Ala Leu Gly Pro
130 135 140

Gly Val Val Gly Ile His Gly Asp Ser Pro Tyr Tyr Phe Leu Thr Ser
145 150 155 160

Ala Phe Leu Thr Ala Ala Ile Ile Leu Leu His Thr Phe Trp Gly Val
165 170 175

Val Phe Phe Asp Ala Cys Glu Arg Arg Arg Tyr Trp Ala Leu Gly Leu
180 185 190

Val Val Gly Ser His Leu Leu Thr Ser Gly Leu Thr Phe Leu Asn Pro
195 200 205

Trp Tyr Glu Ala Ser Leu Leu Pro Ile Tyr Ala Val Thr Val Ser Met
210 215 220

Gly Leu Trp Ala Phe Ile Thr Ala Gly Gly Ser Leu Arg Ser Ile Gln
225 230 235 240

Arg Ser Leu Leu Cys Arg Arg Gln Glu Asp Ser Arg Val Met Val Tyr
245 250 255

Ser Ala Leu Arg Ile Pro Pro Glu Asp
260 265

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<222> (175)..(1602)
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cggctcatca gtcggtccgc gccttgcagc tcctccagag ggacgcgccc cgag atg 177
Met
1

gag agc aaa gcc ctg ctc gtg ctg act ctg gcc gtg tgg ctc cag agt 225

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Glu Ser Lys Ala Leu Leu Val Leu Thr Leu Ala Val Trp Leu Gln Ser
                5                  10                  15

ctg acc gcc tcc cgc gga ggg gtg gcc gcc gcc gac caa aga aga gat      273
Leu Thr Ala Ser Arg Gly Gly Val Ala Ala Ala Asp Gln Arg Arg Asp
            20                  25                  30

ttt atc gac atc gaa agt aaa ttt gcc cta agg acc cct gaa gac aca      321
Phe Ile Asp Ile Glu Ser Lys Phe Ala Leu Arg Thr Pro Glu Asp Thr
        35                  40                  45

gct gag gac act tgc cac ctc att ccc gga gta gca gag tcc gtg gct      369
Ala Glu Asp Thr Cys His Leu Ile Pro Gly Val Ala Glu Ser Val Ala
    50                  55                  60                  65

acc tgt cat ttc aat cac agc agc aaa acc ttc atg gtg atc cat ggc      417
Thr Cys His Phe Asn His Ser Ser Lys Thr Phe Met Val Ile His Gly
                70                  75                  80

tgg acg gta aca gga atg tat gag agt tgg gtg cca aaa ctt gtg gcc      465
Trp Thr Val Thr Gly Met Tyr Glu Ser Trp Val Pro Lys Leu Val Ala
            85                  90                  95

gcc ctg tac aag aga gaa cca gac tcc aat gtc att gtg gtg gac tgg      513
Ala Leu Tyr Lys Arg Glu Pro Asp Ser Asn Val Ile Val Val Asp Trp
        100                 105                 110

ctg tca cgg gct cag gag cat tac cca gtg tcc gcg ggc tac acc aaa      561
Leu Ser Arg Ala Gln Glu His Tyr Pro Val Ser Ala Gly Tyr Thr Lys
    115                 120                 125

ctg gtg gga cag gat gtg gcc cgg ttt atc aac tgg atg gag gag gag      609
Leu Val Gly Gln Asp Val Ala Arg Phe Ile Asn Trp Met Glu Glu Glu
130                 135                 140                 145

ttt aac tac cct ctg gac aat gtc cat ctc ttg gga tac agc ctt gga      657
Phe Asn Tyr Pro Leu Asp Asn Val His Leu Leu Gly Tyr Ser Leu Gly
                150                 155                 160

gcc cat gct gct ggc att gca gga agt ctg acc aat aag aaa gtc aac      705
Ala His Ala Ala Gly Ile Ala Gly Ser Leu Thr Asn Lys Lys Val Asn
            165                 170                 175

aga att act ggc ctc gat cca gct gga cct aac ttt gag tat gca gaa      753
Arg Ile Thr Gly Leu Asp Pro Ala Gly Pro Asn Phe Glu Tyr Ala Glu
        180                 185                 190

gcc ccg agt cgt ctt tct cct gat gat gca gat ttt gta gac gtc tta      801
Ala Pro Ser Arg Leu Ser Pro Asp Asp Ala Asp Phe Val Asp Val Leu
    195                 200                 205

cac aca ttc acc aga ggg tcc cct ggt cga agc att gga atc cag aaa      849
His Thr Phe Thr Arg Gly Ser Pro Gly Arg Ser Ile Gly Ile Gln Lys
210                 215                 220                 225

cca gtt ggg cat gtt gac att tac ccg aat gga ggt act ttt cag cca      897
Pro Val Gly His Val Asp Ile Tyr Pro Asn Gly Gly Thr Phe Gln Pro
                230                 235                 240

gga tgt aac att gga gaa gct atc cgc gtg att gca gag aga gga ctt      945
Gly Cys Asn Ile Gly Glu Ala Ile Arg Val Ile Ala Glu Arg Gly Leu
            245                 250                 255

gga gat gtg gac cag cta gtg aag tgc tcc cac gag cgc tcc att cat      993
Gly Asp Val Asp Gln Leu Val Lys Cys Ser His Glu Arg Ser Ile His
        260                 265                 270

ctc ttc atc gac tct ctg ttg aat gaa gaa aat cca agt aag gcc tac     1041
Leu Phe Ile Asp Ser Leu Leu Asn Glu Glu Asn Pro Ser Lys Ala Tyr
    275                 280                 285

agg tgc agt tcc aag gaa gcc ttt gag aaa ggg ctc tgc ttg agt tgt     1089
Arg Cys Ser Ser Lys Glu Ala Phe Glu Lys Gly Leu Cys Leu Ser Cys
290                 295                 300                 305

aga aag aac cgc tgc aac aat ctg ggc tat gag atc aat aaa gtc aga     1137
Arg Lys Asn Arg Cys Asn Asn Leu Gly Tyr Glu Ile Asn Lys Val Arg
                310                 315                 320

gcc aaa aga agc agc aaa atg tac ctg aag act cgt tct cag atg ccc     1185
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Ala Lys Arg Ser Ser Lys Met Tyr Leu Lys Thr Arg Ser Gln Met Pro
                325                 330                 335

tac aaa gtc ttc cat tac caa gta aag att cat ttt tct ggg act gag      1233
Tyr Lys Val Phe His Tyr Gln Val Lys Ile His Phe Ser Gly Thr Glu
        340                 345                 350

agt gaa acc cat acc aat cag gcc ttt gag att tct ctg tat ggc acc      1281
Ser Glu Thr His Thr Asn Gln Ala Phe Glu Ile Ser Leu Tyr Gly Thr
    355                 360                 365

gtg gcc gag agt gag aac atc cca ttc act ctg cct gaa gtt tcc aca      1329
Val Ala Glu Ser Glu Asn Ile Pro Phe Thr Leu Pro Glu Val Ser Thr
370                 375                 380                 385

aat aag acc tac tcc ttc cta att tac aca gag gta gat att gga gaa      1377
Asn Lys Thr Tyr Ser Phe Leu Ile Tyr Thr Glu Val Asp Ile Gly Glu
                390                 395                 400

cta ctc atg ttg aag ctc aaa tgg aag agt gat tca tac ttt agc tgg      1425
Leu Leu Met Leu Lys Leu Lys Trp Lys Ser Asp Ser Tyr Phe Ser Trp
            405                 410                 415

tca gac tgg tgg agc agt ccc ggc ttc gcc att cag aag atc aga gta      1473
Ser Asp Trp Trp Ser Ser Pro Gly Phe Ala Ile Gln Lys Ile Arg Val
        420                 425                 430

aaa gca gga gag act cag aaa aag gtg atc ttc tgt tct agg gag aaa      1521
Lys Ala Gly Glu Thr Gln Lys Lys Val Ile Phe Cys Ser Arg Glu Lys
    435                 440                 445

gtg tct cat ttg cag aaa gga aag gca cct gcg gta ttt gtg aaa tgc      1569
Val Ser His Leu Gln Lys Gly Lys Ala Pro Ala Val Phe Val Lys Cys
450                 455                 460                 465

cat gac aag tct ctg aat aag aag tca ggc tga aactgggcga atctacagaa    1622
His Asp Lys Ser Leu Asn Lys Lys Ser Gly
                470                 475

caaagaacgg catgtgaatt ctgtgaagaa tgaagtggag gaagtaactt ttacaaaaca    1682

tacccagtgt ttggggtgtt tcaaaagtgg attttcctga atattaatcc cagccctacc    1742

cttgttagtt attttaggag acagtctcaa gcactaaaaa gtggctaatt caatttatgg    1802

ggtatagtgg ccaaatagca catcctccaa cgttaaaaga cagtggatca tgaaaagtgc    1862

tgttttgtcc tttgagaaag aaataattgt ttgagcgcag agtaaaataa ggctccttca    1922

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ggatctttcg gactgaggcc ttctcaaact ttactctaag tctccaagaa tacagaaaat    2042

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ctaatcaaga gtgagtgaac aactatttat aaactagatc tcctatttttt cagaatgctc    2822

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agtgatggtc tcacagagcc aactcactct tatgaaatgg gctttaacaa aacaagaaag 3482
aaacgtactt aactgtgtga agaaatggaa tcagctttta ataaaattga caacatttta 3542
ttaccac 3549

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Met Glu Ser Lys Ala Leu Leu Val Leu Thr Leu Ala Val Trp Leu Gln
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Ser Leu Thr Ala Ser Arg Gly Gly Val Ala Ala Ala Asp Gln Arg Arg
20 25 30

Asp Phe Ile Asp Ile Glu Ser Lys Phe Ala Leu Arg Thr Pro Glu Asp
35 40 45

Thr Ala Glu Asp Thr Cys His Leu Ile Pro Gly Val Ala Glu Ser Val
50 55 60

Ala Thr Cys His Phe Asn His Ser Ser Lys Thr Phe Met Val Ile His
65 70 75 80

Gly Trp Thr Val Thr Gly Met Tyr Glu Ser Trp Val Pro Lys Leu Val
85 90 95

Ala Ala Leu Tyr Lys Arg Glu Pro Asp Ser Asn Val Ile Val Val Asp
100 105 110

Trp Leu Ser Arg Ala Gln Glu His Tyr Pro Val Ser Ala Gly Tyr Thr
115 120 125

Lys Leu Val Gly Gln Asp Val Ala Arg Phe Ile Asn Trp Met Glu Glu
130 135 140

Glu Phe Asn Tyr Pro Leu Asp Asn Val His Leu Leu Gly Tyr Ser Leu
145 150 155 160

Gly Ala His Ala Ala Gly Ile Ala Gly Ser Leu Thr Asn Lys Lys Val
165 170 175

Asn Arg Ile Thr Gly Leu Asp Pro Ala Gly Pro Asn Phe Glu Tyr Ala
180 185 190

Glu Ala Pro Ser Arg Leu Ser Pro Asp Asp Ala Asp Phe Val Asp Val
195 200 205

Leu His Thr Phe Thr Arg Gly Ser Pro Gly Arg Ser Ile Gly Ile Gln
210 215 220

Lys Pro Val Gly His Val Asp Ile Tyr Pro Asn Gly Gly Thr Phe Gln
225 230 235 240

Pro Gly Cys Asn Ile Gly Glu Ala Ile Arg Val Ile Ala Glu Arg Gly
245 250 255

Leu Gly Asp Val Asp Gln Leu Val Lys Cys Ser His Glu Arg Ser Ile
260 265 270

His Leu Phe Ile Asp Ser Leu Leu Asn Glu Glu Asn Pro Ser Lys Ala
275 280 285

Tyr Arg Cys Ser Ser Lys Glu Ala Phe Glu Lys Gly Leu Cys Leu Ser
290 295 300

Cys Arg Lys Asn Arg Cys Asn Asn Leu Gly Tyr Glu Ile Asn Lys Val
305 310 315 320

Arg Ala Lys Arg Ser Ser Lys Met Tyr Leu Lys Thr Arg Ser Gln Met
325 330 335

Pro Tyr Lys Val Phe His Tyr Gln Val Lys Ile His Phe Ser Gly Thr
340 345 350

Glu Ser Glu Thr His Thr Asn Gln Ala Phe Glu Ile Ser Leu Tyr Gly
355 360 365

Thr Val Ala Glu Ser Glu Asn Ile Pro Phe Thr Leu Pro Glu Val Ser
370 375 380

Thr Asn Lys Thr Tyr Ser Phe Leu Ile Tyr Thr Glu Val Asp Ile Gly
385 390 395 400

Glu Leu Leu Met Leu Lys Leu Lys Trp Lys Ser Asp Ser Tyr Phe Ser
405 410 415

Trp Ser Asp Trp Trp Ser Ser Pro Gly Phe Ala Ile Gln Lys Ile Arg
420 425 430

Val Lys Ala Gly Glu Thr Gln Lys Lys Val Ile Phe Cys Ser Arg Glu
435 440 445

Lys Val Ser His Leu Gln Lys Gly Lys Ala Pro Ala Val Phe Val Lys
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Cys His Asp Lys Ser Leu Asn Lys Lys Ser Gly
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gcg ccg ccc ggg ccg ccg tgg ccg ctg ctg ctg ctg ctg ctg ctg ctg      105
Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu Leu Leu Leu
    5                  10                  15

ctg gcg ctg tgc ggc tgc ccg gcc ccc gcc gcg gcc tcg ccg ctc ctg      153
Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser Pro Leu Leu
20                  25                  30                  35

cta ttt gcc aac cgc cgg gac gta cgg ctg gtg gac gcc ggc gga gtc      201
Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala Gly Gly Val
                40                  45                  50

aag ctg gag tcc acc atc gtg gtc agc ggc ctg gag gat gcg gcc gca      249
Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp Ala Ala Ala
            55                  60                  65

gtg gac ttc cag ttt tcc aag gga gcc gtg tac tgg aca gac gtg agc      297
Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr Asp Val Ser
        70                  75                  80

gag gag gcc atc aag cag acc tac ctg aac cag acg ggg gcc gcc gtg      345
Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly Ala Ala Val
    85                  90                  95

cag aac gtg gtc atc tcc ggc ctg gtc tct ccc gac ggc ctc gcc tgc      393
Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly Leu Ala Cys
100                 105                 110                 115

gac tgg gtg ggc aag aag ctg tac tgg acg gac tca gag acc aac cgc      441
Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu Thr Asn Arg
                120                 125                 130

atc gag gtg gcc aac ctc aat ggc aca tcc cgg aag gtg ctc ttc tgg      489
Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val Leu Phe Trp
            135                 140                 145

cag gac ctt gac cag ccg agg gcc atc gcc ttg gac ccc gct cac ggg      537
Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro Ala His Gly
        150                 155                 160

tac atg tac tgg aca gac tgg ggt gag acg ccc cgg att gag cgg gca      585
Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile Glu Arg Ala
    165                 170                 175

ggg atg gat ggc agc acc cgg aag atc att gtg gac tcg gac att tac      633
Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser Asp Ile Tyr
180                 185                 190                 195

tgg ccc aat gga ctg acc atc gac ctg gag gag cag aag ctc tac tgg      681
Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys Leu Tyr Trp
                200                 205                 210

gct gac gcc aag ctc agc ttc atc cac cgt gcc aac ctg gac ggc tcg      729
Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu Asp Gly Ser
            215                 220                 225

ttc cgg cag aag gtg gtg gag ggc agc ctg acg cac ccc ttc gcc ctg      777
Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro Phe Ala Leu
        230                 235                 240

acg ctc tcc ggg gac act ctg tac tgg aca gac tgg cag acc cgc tcc      825
Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln Thr Arg Ser
    245                 250                 255

atc cat gcc tgc aac aag cgc act ggg ggg aag agg aag gag atc ctg      873
Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys Glu Ile Leu
260                 265                 270                 275

agt gcc ctc tac tca ccc atg gac atc cag gtg ctg agc cag gag cgg      921
Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser Gln Glu Arg
                280                 285                 290

cag cct ttc ttc cac act cgc tgt gag gag gac aat ggc ggc tgc tcc      969
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Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly Gly Cys Ser
                295                 300                 305

cac ctg tgc ctg ctg tcc cca agc gag cct ttc tac aca tgc gcc tgc      1017
His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr Cys Ala Cys
        310                 315                 320

ccc acg ggt gtg cag ctg cag gac aac ggc agg acg tgt aag gca gga      1065
Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys Lys Ala Gly
    325                 330                 335

gcc gag gag gtg ctg ctg ctg gcc cgg cgg acg gac cta cgg agg atc      1113
Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu Arg Arg Ile
340                 345                 350                 355

tcg ctg gac acg ccg gac ttt acc gac atc gtg ctg cag gtg gac gac      1161
Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln Val Asp Asp
                360                 365                 370

atc cgg cac gcc att gcc atc gac tac gac ccg cta gag ggc tat gtc      1209
Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu Gly Tyr Val
            375                 380                 385

tac tgg aca gat gac gag gtg cgg gcc atc cgc agg gcg tac ctg gac      1257
Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala Tyr Leu Asp
        390                 395                 400

ggg tct ggg gcg cag acg ctg gtc aac acc gag atc aac gac ccc gat      1305
Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn Asp Pro Asp
    405                 410                 415

ggc atc gcg gtc gac tgg gtg gcc cga aac ctc tac tgg acc gac acg      1353
Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr Asp Thr
420                 425                 430                 435

ggc acg gac cgc atc gag gtg acg cgc ctc aac ggc acc tcc cgc aag      1401
Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr Ser Arg Lys
                440                 445                 450

atc ctg gtg tcg gag gac ctg gac gag ccc cga gcc atc gca ctg cac      1449
Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile Ala Leu His
            455                 460                 465

ccc gtg atg ggc ctc atg tac tgg aca gac tgg gga gag aac cct aaa      1497
Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu Asn Pro Lys
        470                 475                 480

atc gag tgt gcc aac ttg gat ggg cag gag cgg cgt gtg ctg gtc aat      1545
Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val Leu Val Asn
    485                 490                 495

gcc tcc ctc ggg tgg ccc aac ggc ctg gcc ctg gac ctg cag gag ggg      1593
Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu Gln Glu Gly
500                 505                 510                 515

aag ctc tac tgg gga gac gcc aag aca gac aag atc gag gtg atc aat      1641
Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu Val Ile Asn
                520                 525                 530

gtt gat ggg acg aag agg cgg acc ctc ctg gag gac aag ctc ccg cac      1689
Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys Leu Pro His
            535                 540                 545

att ttc ggg ttc acg ctg ctg ggg gac ttc atc tac tgg act gac tgg      1737
Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp Thr Asp Trp
        550                 555                 560

cag cgc cgc agc atc gag cgg gtg cac aag gtc aag gcc agc cgg gac      1785
Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala Ser Arg Asp
    565                 570                 575

gtc atc att gac cag ctg ccc gac ctg atg ggg ctc aaa gct gtg aat      1833
Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys Ala Val Asn
580                 585                 590                 595

gtg gcc aag gtc gtc gga acc aac ccg tgt gcg gac agg aac ggg ggg      1881
Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg Asn Gly Gly
                600                 605                 610

tgc agc cac ctg tgc ttc ttc aca ccc cac gca acc cgg tgt ggc tgc      1929
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Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg Cys Gly Cys
            615                 620                 625

ccc atc ggc ctg gag ctg ctg agt gac atg aag acc tgc atc gtg cct      1977
Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys Ile Val Pro
        630                 635                 640

gag gcc ttc ttg gtc ttc acc agc aga gcc gcc atc cac agg atc tcc      2025
Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His Arg Ile Ser
    645                 650                 655

ctc gag acc aat aac aac gac gtg gcc atc ccg ctc acg ggc gtc aag      2073
Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr Gly Val Lys
660                 665                 670                 675

gag gcc tca gcc ctg gac ttt gat gtg tcc aac aac cac atc tac tgg      2121
Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His Ile Tyr Trp
                680                 685                 690

aca gac gtc agc ctg aag acc atc agc cgc gcc ttc atg aac ggg agc      2169
Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met Asn Gly Ser
            695                 700                 705

tcg gtg gag cac gtg gtg gag ttt ggc ctt gac tac ccc gag ggc atg      2217
Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro Glu Gly Met
        710                 715                 720

gcc gtt gac tgg atg ggc aag aac ctc tac tgg gcc gac act ggg acc      2265
Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp Thr Gly Thr
    725                 730                 735

aac aga atc gaa gtg gcg cgg ctg gac ggg cag ttc cgg caa gtc ctc      2313
Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg Gln Val Leu
740                 745                 750                 755

gtg tgg agg gac ttg gac aac ccg agg tcg ctg gcc ctg gat ccc acc      2361
Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu Asp Pro Thr
                760                 765                 770

aag ggc tac atc tac tgg acc gag tgg ggc ggc aag ccg agg atc gtg      2409
Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro Arg Ile Val
            775                 780                 785

cgg gcc ttc atg gac ggg acc aac tgc atg acg ctg gtg gac aag gtg      2457
Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val Asp Lys Val
        790                 795                 800

ggc cgg gcc aac gac ctc acc att gac tac gct gac cag cgc ctc tac      2505
Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln Arg Leu Tyr
    805                 810                 815

tgg acc gac ctg gac acc aac atg atc gag tcg tcc aac atg ctg ggt      2553
Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn Met Leu Gly
820                 825                 830                 835

cag gag cgg gtc gtg att gcc gac gat ctc ccg cac ccg ttc ggt ctg      2601
Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro Phe Gly Leu
                840                 845                 850

acg cag tac agc gat tat atc tac tgg aca gac tgg aat ctg cac agc      2649
Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn Leu His Ser
            855                 860                 865

att gag cgg gcc gac aag act agc ggc cgg aac cgc acc ctc atc cag      2697
Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr Leu Ile Gln
        870                 875                 880

ggc cac ctg gac ttc gtg atg gac atc ctg gtg ttc cac tcc tcc cgc      2745
Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His Ser Ser Arg
    885                 890                 895

cag gat ggc ctc aat gac tgt atg cac aac aac ggg cag tgt ggg cag      2793
Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln Cys Gly Gln
900                 905                 910                 915

ctg tgc ctt gcc atc ccc ggc ggc cac cgc tgc ggc tgc gcc tca cac      2841
Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys Ala Ser His
                920                 925                 930

tac acc ctg gac ccc agc agc cgc aac tgc agc ccg ccc acc acc ttc      2889
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Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro Thr Thr Phe
                935                 940                 945

ttg ctg ttc agc cag aaa tct gcc atc agt cgg atg atc ccg gac gac      2937
Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile Pro Asp Asp
            950                 955                 960

cag cac agc ccg gat ctc atc ctg ccc ctg cat gga ctg agg aac gtc      2985
Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu Arg Asn Val
        965                 970                 975

aaa gcc atc gac tat gac cca ctg gac aag ttc atc tac tgg gtg gat      3033
Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr Trp Val Asp
    980                 985                 990                 995

ggg cgc cag aac atc  aag cga gcc aag gac  gac ggg acc cag ccc      3078
Gly Arg Gln Asn Ile  Lys Arg Ala Lys Asp  Asp Gly Thr Gln Pro
                1000                1005                1010

ttt gtt ttg acc tct  ctg agc caa ggc caa  aac cca gac agg cag      3123
Phe Val Leu Thr Ser  Leu Ser Gln Gly Gln  Asn Pro Asp Arg Gln
                1015                1020                1025

ccc cac gac ctc agc  atc gac atc tac agc  cgg aca ctg ttc tgg      3168
Pro His Asp Leu Ser  Ile Asp Ile Tyr Ser  Arg Thr Leu Phe Trp
                1030                1035                1040

acg tgc gag gcc acc  aat acc atc aac gtc  cac agg ctg agc ggg      3213
Thr Cys Glu Ala Thr  Asn Thr Ile Asn Val  His Arg Leu Ser Gly
                1045                1050                1055

gaa gcc atg ggg gtg  gtg ctg cgt ggg gac  cgc gac aag ccc agg      3258
Glu Ala Met Gly Val  Val Leu Arg Gly Asp  Arg Asp Lys Pro Arg
                1060                1065                1070

gcc atc gtc gtc aac  gcg gag cga ggg tac  ctg tac ttc acc aac      3303
Ala Ile Val Val Asn  Ala Glu Arg Gly Tyr  Leu Tyr Phe Thr Asn
                1075                1080                1085

atg cag gac cgg gca  gcc aag atc gaa cgc  gca gcc ctg gac ggc      3348
Met Gln Asp Arg Ala  Ala Lys Ile Glu Arg  Ala Ala Leu Asp Gly
                1090                1095                1100

acc gag cgc gag gtc  ctc ttc acc acc ggc  ctc atc cgc cct gtg      3393
Thr Glu Arg Glu Val  Leu Phe Thr Thr Gly  Leu Ile Arg Pro Val
                1105                1110                1115

gcc ctg gtg gta gac  aac aca ctg ggc aag  ctg ttc tgg gtg gac      3438
Ala Leu Val Val Asp  Asn Thr Leu Gly Lys  Leu Phe Trp Val Asp
                1120                1125                1130

gcg gac ctg aag cgc  att gag agc tgt gac  ctg tca ggg gcc aac      3483
Ala Asp Leu Lys Arg  Ile Glu Ser Cys Asp  Leu Ser Gly Ala Asn
                1135                1140                1145

cgc ctg acc ctg gag  gac gcc aac atc gtg  cag cct ctg ggc ctg      3528
Arg Leu Thr Leu Glu  Asp Ala Asn Ile Val  Gln Pro Leu Gly Leu
                1150                1155                1160

acc atc ctt ggc aag  cat ctc tac tgg atc  gac cgc cag cag cag      3573
Thr Ile Leu Gly Lys  His Leu Tyr Trp Ile  Asp Arg Gln Gln Gln
                1165                1170                1175

atg atc gag cgt gtg  gag aag acc acc ggg  gac aag cgg act cgc      3618
Met Ile Glu Arg Val  Glu Lys Thr Thr Gly  Asp Lys Arg Thr Arg
                1180                1185                1190

atc cag ggc cgt gtc  gcc cac ctc act ggc  atc cat gca gtg gag      3663
Ile Gln Gly Arg Val  Ala His Leu Thr Gly  Ile His Ala Val Glu
                1195                1200                1205

gaa gtc agc ctg gag  gag ttc tca gcc cac  cca tgt gcc cgt gac      3708
Glu Val Ser Leu Glu  Glu Phe Ser Ala His  Pro Cys Ala Arg Asp
                1210                1215                1220

aat ggt ggc tgc tcc  cac atc tgt att gcc  aag ggt gat ggg aca      3753
Asn Gly Gly Cys Ser  His Ile Cys Ile Ala  Lys Gly Asp Gly Thr
                1225                1230                1235

cca cgg tgc tca tgc  cca gtc cac ctc gtg  ctc ctg cag aac ctg      3798
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Pro Arg Cys Ser Cys  Pro Val His Leu Val  Leu Leu Gln Asn Leu
                1240                1245                1250

ctg acc tgt gga gag  ccg ccc acc tgc tcc  ccg gac cag ttt gca      3843
Leu Thr Cys Gly Glu  Pro Pro Thr Cys Ser  Pro Asp Gln Phe Ala
                1255                1260                1265

tgt gcc aca ggg gag  atc gac tgt atc ccc  ggg gcc tgg cgc tgt      3888
Cys Ala Thr Gly Glu  Ile Asp Cys Ile Pro  Gly Ala Trp Arg Cys
                1270                1275                1280

gac ggc ttt ccc gag  tgc gat gac cag agc  gac gag gag ggc tgc      3933
Asp Gly Phe Pro Glu  Cys Asp Asp Gln Ser  Asp Glu Glu Gly Cys
                1285                1290                1295

ccc gtg tgc tcc gcc  gcc cag ttc ccc tgc  gcg cgg ggt cag tgt      3978
Pro Val Cys Ser Ala  Ala Gln Phe Pro Cys  Ala Arg Gly Gln Cys
                1300                1305                1310

gtg gac ctg cgc ctg  cgc tgc gac ggc gag  gca gac tgt cag gac      4023
Val Asp Leu Arg Leu  Arg Cys Asp Gly Glu  Ala Asp Cys Gln Asp
                1315                1320                1325

cgc tca gac gag gcg  gac tgt gac gcc atc  tgc ctg ccc aac cag      4068
Arg Ser Asp Glu Ala  Asp Cys Asp Ala Ile  Cys Leu Pro Asn Gln
                1330                1335                1340

ttc cgg tgt gcg agc  ggc cag tgt gtc ctc  atc aaa cag cag tgc      4113
Phe Arg Cys Ala Ser  Gly Gln Cys Val Leu  Ile Lys Gln Gln Cys
                1345                1350                1355

gac tcc ttc ccc gac  tgt atc gac ggc tcc  gac gag ctc atg tgt      4158
Asp Ser Phe Pro Asp  Cys Ile Asp Gly Ser  Asp Glu Leu Met Cys
                1360                1365                1370

gaa atc acc aag ccg  ccc tca gac gac agc  ccg gcc cac agc agt      4203
Glu Ile Thr Lys Pro  Pro Ser Asp Asp Ser  Pro Ala His Ser Ser
                1375                1380                1385

gcc atc ggg ccc gtc  att ggc atc atc ctc  tct ctc ttc gtc atg      4248
Ala Ile Gly Pro Val  Ile Gly Ile Ile Leu  Ser Leu Phe Val Met
                1390                1395                1400

ggt ggt gtc tat ttt  gtg tgc cag cgc gtg  gtg tgc cag cgc tat      4293
Gly Gly Val Tyr Phe  Val Cys Gln Arg Val  Val Cys Gln Arg Tyr
                1405                1410                1415

gcg ggg gcc aac ggg  ccc ttc ccg cac gag  tat gtc agc ggg acc      4338
Ala Gly Ala Asn Gly  Pro Phe Pro His Glu  Tyr Val Ser Gly Thr
                1420                1425                1430

ccg cac gtg ccc ctc  aat ttc ata gcc ccg  ggc ggt tcc cag cat      4383
Pro His Val Pro Leu  Asn Phe Ile Ala Pro  Gly Gly Ser Gln His
                1435                1440                1445

ggc ccc ttc aca ggc  atc gca tgc gga aag  tcc atg atg agc tcc      4428
Gly Pro Phe Thr Gly  Ile Ala Cys Gly Lys  Ser Met Met Ser Ser
                1450                1455                1460

gtg agc ctg atg ggg  ggc cgg ggc ggg gtg  ccc ctc tac gac cgg      4473
Val Ser Leu Met Gly  Gly Arg Gly Gly Val  Pro Leu Tyr Asp Arg
                1465                1470                1475

aac cac gtc aca ggg  gcc tcg tcc agc agc  tcg tcc agc acg aag      4518
Asn His Val Thr Gly  Ala Ser Ser Ser Ser  Ser Ser Ser Thr Lys
                1480                1485                1490

gcc acg ctg tac ccg  ccg atc ctg aac ccg  ccg ccc tcc ccg gcc      4563
Ala Thr Leu Tyr Pro  Pro Ile Leu Asn Pro  Pro Pro Ser Pro Ala
                1495                1500                1505

acg gac ccc tcc ctg  tac aac atg gac atg  ttc tac tct tca aac      4608
Thr Asp Pro Ser Leu  Tyr Asn Met Asp Met  Phe Tyr Ser Ser Asn
                1510                1515                1520

att ccg gcc act gtg  aga ccg tac agg ccc  tac atc att cga gga      4653
Ile Pro Ala Thr Val  Arg Pro Tyr Arg Pro  Tyr Ile Ile Arg Gly
                1525                1530                1535

atg gcg ccc ccg acg  acg ccc tgc agc acc  gac gtg tgt gac agc      4698
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Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp Ser
                1540                1545                1550

gac tac agc gcc agc cgc tgg aag gcc agc aag tac tac ctg gat      4743
Asp Tyr Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr Leu Asp
                1555                1560                1565

ttg aac tcg gac tca gac ccc tat cca ccc cca ccc acg ccc cac      4788
Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro His
                1570                1575                1580

agc cag tac ctg tcg gcg gag gac agc tgc ccg ccc tcg ccc gcc      4833
Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro Ala
                1585                1590                1595

acc gag agg agc tac ttc cat ctc ttc ccg ccc cct ccg tcc ccc      4878
Thr Glu Arg Ser Tyr Phe His Leu Phe Pro Pro Pro Pro Ser Pro
                1600                1605                1610

tgc acg gac tca tcc tga cctcggccgg gccactctgg cttctctgtg          4926
Cys Thr Asp Ser Ser
                1615

cccctgtaaa tagttttaaa tatgaacaaa gaaaaaaata tattttatga tttaaaaaat  4986

aaatataatt gggattttaa aaacatgaga aatgtgaact gtgatggggt gggcagggct  5046

gggagaactt tgtacagtgg aacaaatatt tataaactta attttgtaaa acag        5100
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<210> 50
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Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu
1               5                  10                  15

Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser
            20                  25                  30

Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala
        35                  40                  45

Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp
    50                  55                  60

Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr
65                  70                  75                  80

Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly
                85                  90                  95

Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly
            100                 105                 110

Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu
        115                 120                 125

Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val
    130                 135                 140

Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro
145                 150                 155                 160

Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile
                165                 170                 175
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Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser
180 185 190

Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys
195 200 205

Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu
210 215 220

Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro
225 230 235 240

Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln
245 250 255

Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys
260 265 270

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser
275 280 285

Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly
290 295 300

Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr
305 310 315 320

Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys
325 330 335

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu
340 345 350

Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln
355 360 365

Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu
370 375 380

Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala
385 390 395 400

Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn
405 410 415

Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp
420 425 430

Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr
435 440 445

Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile
450 455 460

Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu
465 470 475 480

Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val
485 490 495

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu
500 505 510

Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu
515 520 525

Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys
530 535 540

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp
545 550 555 560

Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala
565 570 575

Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys
580 585 590

Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg
595 600 605

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg
610 615 620

Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys
625 630 635 640

Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His
645 650 655

Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr
660 665 670

Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His
675 680 685

Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met
690 695 700

Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro
705 710 715 720

Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp
725 730 735

Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg
740 745 750

Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu
755 760 765

Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro
770 775 780

Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val
785 790 795 800

Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln
805 810 815

Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn
820 825 830

Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro
835 840 845

Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn
850 855 860

Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr
865 870 875 880

Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His
885 890 895

Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln
900 905 910

Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys
915 920 925

Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro
930 935 940

Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile
945 950 955 960

Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu
965 970 975

Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr
980 985 990

Trp Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr
995 1000 1005

Gln Pro Phe Val Leu Thr Ser Leu Ser Gln Gly Gln Asn Pro Asp
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Arg Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu
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Phe Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu
1040 1045 1050

Ser Gly Glu Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys
1055 1060 1065

Pro Arg Ala Ile Val Val Asn Ala Glu Arg Gly Tyr Leu Tyr Phe
1070 1075 1080

Thr Asn Met Gln Asp Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu
1085 1090 1095

Asp Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg
1100 1105 1110

Pro Val Ala Leu Val Val Asp Asn Thr Leu Gly Lys Leu Phe Trp
1115 1120 1125

Val Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly
1130 1135 1140

Ala Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Leu
1145 1150 1155

Gly Leu Thr Ile Leu Gly Lys His Leu Tyr Trp Ile Asp Arg Gln
1160 1165 1170

Gln Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg
1175 1180 1185

Thr Arg Ile Gln Gly Arg Val Ala His Leu Thr Gly Ile His Ala
1190 1195 1200

Val Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala
1205 1210 1215

Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp
1220 1225 1230

Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln
1235 1240 1245

Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln
1250 1255 1260

Phe Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp
1265 1270 1275

Arg Cys Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu
1280 1285 1290

Gly Cys Pro Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly
1295 1300 1305

Gln Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys
1310 1315 1320

Gln Asp Arg Ser Asp Glu Ala Asp Cys Asp Ala Ile Cys Leu Pro
1325 1330 1335

Asn Gln Phe Arg Cys Ala Ser Gly Gln Cys Val Leu Ile Lys Gln
1340 1345 1350

Gln Cys Asp Ser Phe Pro Asp Cys Ile Asp Gly Ser Asp Glu Leu
1355 1360 1365

Met Cys Glu Ile Thr Lys Pro Pro Ser Asp Asp Ser Pro Ala His
1370 1375 1380

Ser Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe
1385 1390 1395

Val Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Val Cys Gln
1400 1405 1410

Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His Glu Tyr Val Ser
1415 1420 1425

Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser
1430 1435 1440

Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser Met Met
1445 1450 1455

Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu Tyr
1460 1465 1470

Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser
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Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser
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Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser
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Ser Asn Ile Pro Ala Thr Val Arg Pro Tyr Arg Pro Tyr Ile Ile
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Arg Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys
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Asp Ser Asp Tyr Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr
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Leu Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr
1565 1570 1575

Pro His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser
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Ser Pro Cys Thr Asp Ser Ser
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Leu Leu Leu Leu Ala Val Leu Leu Ala Ala His Pro Asp Ala Gln Ala
20 25 30

gag gtg cgc ttg tct gta ccc ccg ctg gtg gag gtg atg cga gga aag 146
Glu Val Arg Leu Ser Val Pro Pro Leu Val Glu Val Met Arg Gly Lys
35 40 45

tct gtc att ctg gac tgc acc cct acg gga acc cac gac cat tat atg 194
Ser Val Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met
50 55 60

ctg gaa tgg ttc ctt acc gac cgc tcg gga gct cgc ccc cgc cta gcc 242

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Leu Glu Trp Phe Leu Thr Asp Arg Ser Gly Ala Arg Pro Arg Leu Ala
 65                  70                  75

tcg gct gag atg cag ggc tct gag ctc cag gtc aca atg cac gac acc      290
Ser Ala Glu Met Gln Gly Ser Glu Leu Gln Val Thr Met His Asp Thr
80                  85                  90                  95

cgg ggc cgc agt ccc cca tac cag ctg gac tcc cag ggg cgc ctg gtg      338
Arg Gly Arg Ser Pro Pro Tyr Gln Leu Asp Ser Gln Gly Arg Leu Val
                100                 105                 110

ctg gct gag gcc cag gtg ggc gac gag cga gac tac gtg tgc gtg gtg      386
Leu Ala Glu Ala Gln Val Gly Asp Glu Arg Asp Tyr Val Cys Val Val
            115                 120                 125

agg gca ggg gcg gca ggc act gct gag gcc act gcg cgg ctc aac gtg      434
Arg Ala Gly Ala Ala Gly Thr Ala Glu Ala Thr Ala Arg Leu Asn Val
        130                 135                 140

ttt gca aag cca gag gcc act gag gtc tcc ccc aac aaa ggg aca ctg      482
Phe Ala Lys Pro Glu Ala Thr Glu Val Ser Pro Asn Lys Gly Thr Leu
145                 150                 155

tct gtg atg gag gac tct gcc cag gag atc gcc acc tgc aac agc cgg      530
Ser Val Met Glu Asp Ser Ala Gln Glu Ile Ala Thr Cys Asn Ser Arg
160                 165                 170                 175

aac ggg aac ccg gcc ccc aag atc acg tgg tat cgc aac ggg cag cgc      578
Asn Gly Asn Pro Ala Pro Lys Ile Thr Trp Tyr Arg Asn Gly Gln Arg
                180                 185                 190

ctg gag gtg ccc gta gag atg aac cca gag ggc tac atg acc agc cgc      626
Leu Glu Val Pro Val Glu Met Asn Pro Glu Gly Tyr Met Thr Ser Arg
            195                 200                 205

acg gtc cgg gag gcc tcg ggc ctg ctc tcc ctc acc agc acc ctc tac      674
Thr Val Arg Glu Ala Ser Gly Leu Leu Ser Leu Thr Ser Thr Leu Tyr
        210                 215                 220

ctg cgg ctc cgc aag gat gac cga gac gcc agc ttc cac tgc gcc gcc      722
Leu Arg Leu Arg Lys Asp Asp Arg Asp Ala Ser Phe His Cys Ala Ala
225                 230                 235

cac tac agc ctg ccc gag ggc cgc cac ggc cgc ctg gac agc ccc acc      770
His Tyr Ser Leu Pro Glu Gly Arg His Gly Arg Leu Asp Ser Pro Thr
240                 245                 250                 255

ttc cac ctc acc ctg cac tat ccc acg gag cac gtg cag ttc tgg gtg      818
Phe His Leu Thr Leu His Tyr Pro Thr Glu His Val Gln Phe Trp Val
                260                 265                 270

ggc agc ccg tcc acc cca gca ggc tgg gta cgc gag ggt gac act gtc      866
Gly Ser Pro Ser Thr Pro Ala Gly Trp Val Arg Glu Gly Asp Thr Val
            275                 280                 285

cag ctg ctc tgc cgg ggg gac ggc agc ccc agc ccg gag tat acg ctt      914
Gln Leu Leu Cys Arg Gly Asp Gly Ser Pro Ser Pro Glu Tyr Thr Leu
        290                 295                 300

ttc cgc ctt cag gat gag cag gag gaa gtg ctg aat gtg aat ctc gag      962
Phe Arg Leu Gln Asp Glu Gln Glu Glu Val Leu Asn Val Asn Leu Glu
305                 310                 315

ggg aac ttg acc ctg gag gga gtg acc cgg ggc cag agc ggg acc tat     1010
Gly Asn Leu Thr Leu Glu Gly Val Thr Arg Gly Gln Ser Gly Thr Tyr
320                 325                 330                 335

ggc tgc aga gtg gag gat tac gac gcg gca gat gac gtg cag ctc tcc     1058
Gly Cys Arg Val Glu Asp Tyr Asp Ala Ala Asp Asp Val Gln Leu Ser
                340                 345                 350

aag acg ctg gag ctg cgc gtg gcc tat ctg gac ccc ctg gag ctc agc     1106
Lys Thr Leu Glu Leu Arg Val Ala Tyr Leu Asp Pro Leu Glu Leu Ser
            355                 360                 365

gag ggg aag gtg ctt tcc tta cct cta aac agc agt gca gtc gtg aac     1154
Glu Gly Lys Val Leu Ser Leu Pro Leu Asn Ser Ser Ala Val Val Asn
        370                 375                 380

tgc tcc gtg cac ggc ctg ccc acc cct gcc cta cgc tgg acc aag gac     1202
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Cys Ser Val His Gly Leu Pro Thr Pro Ala Leu Arg Trp Thr Lys Asp
385                 390                 395

tcc act ccc ctg ggc gat ggc ccc atg ctg tcg ctc agt tct atc acc      1250
Ser Thr Pro Leu Gly Asp Gly Pro Met Leu Ser Leu Ser Ser Ile Thr
400                 405                 410                 415

ttc gat tcc aat ggc acc tac gta tgt gag gcc tcc ctg ccc aca gtc      1298
Phe Asp Ser Asn Gly Thr Tyr Val Cys Glu Ala Ser Leu Pro Thr Val
                420                 425                 430

ccg gtc ctc agc cgc acc cag aac ttc acg ctg ctg gtc caa ggc tcg      1346
Pro Val Leu Ser Arg Thr Gln Asn Phe Thr Leu Leu Val Gln Gly Ser
            435                 440                 445

cca gag cta aag aca gcg gaa ata gag ccc aag gca gat ggc agc tgg      1394
Pro Glu Leu Lys Thr Ala Glu Ile Glu Pro Lys Ala Asp Gly Ser Trp
        450                 455                 460

agg gaa gga gac gaa gtc aca ctc atc tgc tct gcc cgc ggc cat cca      1442
Arg Glu Gly Asp Glu Val Thr Leu Ile Cys Ser Ala Arg Gly His Pro
465                 470                 475

gac ccc aaa ctc agc tgg agc caa ttg ggg ggc agc ccc gca gag cca      1490
Asp Pro Lys Leu Ser Trp Ser Gln Leu Gly Gly Ser Pro Ala Glu Pro
480                 485                 490                 495

atc ccc gga cgg cag ggt tgg gtg agc agc tct ctg acc ctg aaa gtg      1538
Ile Pro Gly Arg Gln Gly Trp Val Ser Ser Ser Leu Thr Leu Lys Val
                500                 505                 510

acc agc gcc ctg agc cgc gat ggc atc tcc tgt gaa gcc tcc aac ccc      1586
Thr Ser Ala Leu Ser Arg Asp Gly Ile Ser Cys Glu Ala Ser Asn Pro
            515                 520                 525

cac ggg aac aag cgc cat gtc ttc cac ttc ggc acc gtg agc ccc cag      1634
His Gly Asn Lys Arg His Val Phe His Phe Gly Thr Val Ser Pro Gln
        530                 535                 540

acc tcc cag gct gga gtg gcc gtc atg gcc gtg gcc gtc agc gtg ggc      1682
Thr Ser Gln Ala Gly Val Ala Val Met Ala Val Ala Val Ser Val Gly
545                 550                 555

ctc ctg ctc ctc gtc gtt gct gtc ttc tac tgc gtg aga cgc aaa ggg      1730
Leu Leu Leu Leu Val Val Ala Val Phe Tyr Cys Val Arg Arg Lys Gly
560                 565                 570                 575

ggc ccc tgc tgc cgc cag cgg cgg gag aag ggg gct ccg ccg cca ggg      1778
Gly Pro Cys Cys Arg Gln Arg Arg Glu Lys Gly Ala Pro Pro Pro Gly
                580                 585                 590

gag cca ggg ctg agc cac tcg ggg tcg gag caa cca gag cag acc ggc      1826
Glu Pro Gly Leu Ser His Ser Gly Ser Glu Gln Pro Glu Gln Thr Gly
            595                 600                 605

ctt ctc atg gga ggt gcc tcc gga gga gcc agg ggt ggc agc ggg ggc      1874
Leu Leu Met Gly Gly Ala Ser Gly Gly Ala Arg Gly Gly Ser Gly Gly
        610                 615                 620

ttc gga gac gag tgc tga gccaagaacc tcctagaggc tgtccctgga             1922
Phe Gly Asp Glu Cys
625

cctggagctg caggcatcag agaaccagcc ctgctcacgc catgcccgcc cccgccttcc    1982

ctcttccctc ttccctctcc ctgcccagcc ctcccttcct tcctctgccg gcaaggcagg    2042

gacccacagt ggctgcctgc ctccgggagg gaaggagagg gagggtgggt gggtgggagg    2102

gggccttcct ccagggaatg tgactctccc aggccccaga atagctcctg gacccaagcc    2162

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gcctcccttg ctggtccccc cacctgacgt cttgctgcag agtctgacac tggattcccc    2282

cccctcaccc cgcccctggt cccactcctg cccccgccct acctccgccc caccccatca    2342

tctgtggaca ctggagtctg gaataaatgc tgtttgtcac atcaaaaaaa aaaaaaaaaa    2402

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aaaaaaaaaa aaaaaaa 2479

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Leu Leu Leu Ala Val Leu Leu Ala Ala His Pro Asp Ala Gln Ala Glu
20 25 30

Val Arg Leu Ser Val Pro Pro Leu Val Glu Val Met Arg Gly Lys Ser
35 40 45

Val Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met Leu
50 55 60

Glu Trp Phe Leu Thr Asp Arg Ser Gly Ala Arg Pro Arg Leu Ala Ser
65 70 75 80

Ala Glu Met Gln Gly Ser Glu Leu Gln Val Thr Met His Asp Thr Arg
85 90 95

Gly Arg Ser Pro Pro Tyr Gln Leu Asp Ser Gln Gly Arg Leu Val Leu
100 105 110

Ala Glu Ala Gln Val Gly Asp Glu Arg Asp Tyr Val Cys Val Val Arg
115 120 125

Ala Gly Ala Ala Gly Thr Ala Glu Ala Thr Ala Arg Leu Asn Val Phe
130 135 140

Ala Lys Pro Glu Ala Thr Glu Val Ser Pro Asn Lys Gly Thr Leu Ser
145 150 155 160

Val Met Glu Asp Ser Ala Gln Glu Ile Ala Thr Cys Asn Ser Arg Asn
165 170 175

Gly Asn Pro Ala Pro Lys Ile Thr Trp Tyr Arg Asn Gly Gln Arg Leu
180 185 190

Glu Val Pro Val Glu Met Asn Pro Glu Gly Tyr Met Thr Ser Arg Thr
195 200 205

Val Arg Glu Ala Ser Gly Leu Leu Ser Leu Thr Ser Thr Leu Tyr Leu
210 215 220

Arg Leu Arg Lys Asp Asp Arg Asp Ala Ser Phe His Cys Ala Ala His
225 230 235 240

Tyr Ser Leu Pro Glu Gly Arg His Gly Arg Leu Asp Ser Pro Thr Phe
245 250 255

His Leu Thr Leu His Tyr Pro Thr Glu His Val Gln Phe Trp Val Gly
260 265 270

Ser Pro Ser Thr Pro Ala Gly Trp Val Arg Glu Gly Asp Thr Val Gln
275 280 285

Leu Leu Cys Arg Gly Asp Gly Ser Pro Ser Pro Glu Tyr Thr Leu Phe
290 295 300

Arg Leu Gln Asp Glu Gln Glu Glu Val Leu Asn Val Asn Leu Glu Gly
305 310 315 320

Asn Leu Thr Leu Glu Gly Val Thr Arg Gly Gln Ser Gly Thr Tyr Gly
325 330 335

Cys Arg Val Glu Asp Tyr Asp Ala Ala Asp Asp Val Gln Leu Ser Lys
340 345 350

Thr Leu Glu Leu Arg Val Ala Tyr Leu Asp Pro Leu Glu Leu Ser Glu
355 360 365

Gly Lys Val Leu Ser Leu Pro Leu Asn Ser Ser Ala Val Val Asn Cys
370 375 380

Ser Val His Gly Leu Pro Thr Pro Ala Leu Arg Trp Thr Lys Asp Ser
385 390 395 400

Thr Pro Leu Gly Asp Gly Pro Met Leu Ser Leu Ser Ser Ile Thr Phe
405 410 415

Asp Ser Asn Gly Thr Tyr Val Cys Glu Ala Ser Leu Pro Thr Val Pro
420 425 430

Val Leu Ser Arg Thr Gln Asn Phe Thr Leu Leu Val Gln Gly Ser Pro
435 440 445

Glu Leu Lys Thr Ala Glu Ile Glu Pro Lys Ala Asp Gly Ser Trp Arg
450 455 460

Glu Gly Asp Glu Val Thr Leu Ile Cys Ser Ala Arg Gly His Pro Asp
465 470 475 480

Pro Lys Leu Ser Trp Ser Gln Leu Gly Gly Ser Pro Ala Glu Pro Ile
485 490 495

Pro Gly Arg Gln Gly Trp Val Ser Ser Ser Leu Thr Leu Lys Val Thr
500 505 510

Ser Ala Leu Ser Arg Asp Gly Ile Ser Cys Glu Ala Ser Asn Pro His
515 520 525

Gly Asn Lys Arg His Val Phe His Phe Gly Thr Val Ser Pro Gln Thr
530 535 540

Ser Gln Ala Gly Val Ala Val Met Ala Val Ala Val Ser Val Gly Leu
545 550 555 560

Leu Leu Leu Val Val Ala Val Phe Tyr Cys Val Arg Arg Lys Gly Gly
565 570 575

Pro Cys Cys Arg Gln Arg Arg Glu Lys Gly Ala Pro Pro Pro Gly Glu
580 585 590

Pro Gly Leu Ser His Ser Gly Ser Glu Gln Pro Glu Gln Thr Gly Leu
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Leu Met Gly Gly Ala Ser Gly Gly Ala Arg Gly Gly Ser Gly Gly Phe
610 615 620

Gly Asp Glu Cys
625

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tctcggtgca gcgggacagg gcgaagcggc ctgcgcccac ggagcgcgcg acactgcccg 180

gaagggaccg ccacccttgc cccctcagct gcccactcgt gatttccagc ggcctccgcg 240

cgcgcacg atg ccc tcg gcc acc agc cac agc ggg agc ggc agc aag tcg 290
Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser
1 5 10

tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg agt gag gcg gcc gcg 338
Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala
15 20 25 30

gga gcc ggg gcc gcc gcg ccg gct tct cag cac ccc gca acc ggc acc 386
Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr
35 40 45

ggc gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg atc gac 434
Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp
50 55 60

aag aaa ctt cgg aac ctg gag aag aaa aag ggt aag ctt gat gat tac 482
Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr
65 70 75

cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag ctg gat 530
Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp
80 85 90

gcc gtt tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca aaa 578
Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys
95 100 105 110

gaa tta cag agg agt ttc atg gca cta agt caa gat att cag aaa aca 626
Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr
115 120 125

ata aag aag aca gca cgt cgg gag cag ctt atg aga gaa gaa gct gaa 674
Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu
130 135 140

cag aaa cgt tta aaa act gta ctt gag cta cag tat gtt ttg gac aaa 722
Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys
145 150 155

ttg gga gat gat gaa gtg cgg act gac ctg aaa caa ggt ttg aat gga 770
Leu Gly Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly
160 165 170

gtg cca ata ttg tcc gaa gag gag ttg tca ttg ttg gat gaa ttc tat 818
Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr
175 180 185 190

aag cta gta gac cct gaa cgg gac atg agc ttg agg ttg aat gaa cag 866
Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln
195 200 205

tat gaa cat gcc tcc att cac ctg tgg gac ctg ctg gaa ggg aag gaa 914

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Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu
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aaa cct gta tgt gga acc acc tat aaa gtt cta aag gaa att gtt gag      962
Lys Pro Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu
        225                 230                 235

cgt gtt ttt cag tca aac tac ttt gac agc acc cac aac cac cag aat     1010
Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn
    240                 245                 250

ggg ctg tgt gag gaa gaa gag gca gcc tca gca cct gca gtt gaa gac     1058
Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp
255                 260                 265                 270

cag gta cct gaa gct gaa cct gag cca gca gaa gag tac act gag caa     1106
Gln Val Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln
                275                 280                 285

agt gaa gtt gaa tca aca gag tat gta aat aga cag ttc atg gca gaa     1154
Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu
            290                 295                 300

aca cag ttc acc agt ggt gaa aag gag cag gta gat gag tgg aca gtt     1202
Thr Gln Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val
        305                 310                 315

gaa acg gtt gag gtg gta aat tca ctc cag cag caa cct cag gct gca     1250
Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala
    320                 325                 330

tcc cct tca gta cca gag ccc cac tct ttg act cca gtg gct cag gca     1298
Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala
335                 340                 345                 350

gat ccc ctt gtg aga aga cag cga gta caa gac ctt atg gca caa atg     1346
Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met
                355                 360                 365

cag ggt ccc tat aat ttc ata cag gat tca atg ctg gat ttt gaa aat     1394
Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn
            370                 375                 380

cag aca ctt gat cct gcc att gta tct gca cag cct atg aat cca aca     1442
Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr
        385                 390                 395

caa aac atg gac atg ccc cag ctg gtt tgc cct cca gtt cat tct gaa     1490
Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu
    400                 405                 410

tct aga ctt gct cag cct aat caa gtt cct gta caa cca gaa gcg aca     1538
Ser Arg Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr
415                 420                 425                 430

cag gtt cct ttg gta tca tcc aca agt gag ggg tac aca gca tct caa     1586
Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln
                435                 440                 445

ccc ttg tac cag cct tct cat gct aca gag caa cga cca cag aag gaa     1634
Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu
            450                 455                 460

cca att gat cag att cag gca aca atc tct tta aat aca gac cag act     1682
Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr
        465                 470                 475

aca gca tca tca tcc ctt cct gct gcg tct cag cct caa gta ttt cag     1730
Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln
    480                 485                 490

gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta aat gca     1778
Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala
495                 500                 505                 510

gct cca ttc caa tcc atg caa acg gtg ttc aat atg aat gcc cca gtt     1826
Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val
                515                 520                 525

cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag tac cag     1874
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Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln
                530                 535                 540

gcc agt tat aac cag agc ttt tct agt cag cct cac caa gta gaa caa      1922
Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln
        545                 550                 555

aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act tac cat      1970
Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His
    560                 565                 570

ggt tcc cca gac cag tcc cat caa gtg act ggt aac cac cag cag cct      2018
Gly Ser Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro
575                 580                 585                 590

cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat tac aat      2066
Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn
                595                 600                 605

agt cgt ggt gtg tct cgt gga ggc tcc cgt ggt gct aga ggc ttg atg      2114
Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met
            610                 615                 620

aat gga tac cgg ggc cct gcc aat gga ttc aga gga gga tat gat ggt      2162
Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly
        625                 630                 635

tac cgc cct tca ttc tct aac act cca aac agt ggt tat aca cag tct      2210
Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser
    640                 645                 650

cag ttc agt gct ccc cgg gat tac tct ggc tat caa cgg gat gga tat      2258
Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr
655                 660                 665                 670

cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga gcc      2306
Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala
                675                 680                 685

cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg caa      2354
Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln
            690                 695                 700

atg aac act cag caa gtg aat taa tctgattcac aggattatgt ttaatcgcca      2408
Met Asn Thr Gln Gln Val Asn
        705

aaaacacact ggccagtgta ccataatatg ttaccagaag agttattatc tatttgttct      2468

ccctttcagg aaacttattg taaagggact gttttcatcc cataaagaca ggactacaat      2528

tgtcagcttt ctattacctg gatatggaag gaaactattt ttactctgca tgttctgtcc      2588

taagcgtcat cttgagcctt gcacatgata ctcagattcc tcacccttgc ttaggagtaa      2648

aacaatatac tttacagggt gataataatc tccatagtta tttgaagtgg cttgaaaaag      2708

gcaagattga cttttatgac attggataaa atctacaaat cagccctcga gttattcaat      2768

gataactgac aaactaaatt atttccctag aaaggaagat gaaaggagtg gagtgtggtt      2828

tggcagaaca actgcatttc acagcttttc cagttaaatt ggagcactga acgttcagat      2888

gcataccaaa ttatgcatgg gtcctaatca cacatataag gctggctacc agctttgaca      2948

cagcactgtt catctggcca aacaactgtg gttaaaaaca catgtaaaat gctttttaac      3008

agctgatact gtataagaca aagccaagat gcaaaattag gctttgattg gcacttttg       3068

aaaaatatgc aacaaatatg ggatgtaatc cggatggccg cttctgtact taatgtgaaa      3128

tatttagata ccttttttgaa cacttaacag tttctttgag acaatgactt ttgtaaggat     3188

tggtactatc tatcattcct tatgacatgt acattgtctg tcactaatcc ttggattttg      3248

ctgtattgtc acctaaattg gtacaggtac tgatgaaaat ctctagtgga taatcataac      3308

actctcggtc acatgttttt ccttcagctt gaaagctttt ttttaaaagg aaaagatacc      3368

aaatgcctgc tgctaccacc cttttcaatt gctatctttt gaaaggcacc agtatgtgtt      3428
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ttagattgat ttccctgttt cagggaaatc acggacagta gtttcagttc tgatggtata 3488

agcaaaacaa ataaaacgtt tataaaagtt gtatcttgaa acactggtgt tcaacagcta 3548

gcagcttatg tgattca 3565

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Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
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Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala
35 40 45

Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys
50 55 60

Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu
65 70 75 80

Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val
85 90 95

Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu
100 105 110

Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys
115 120 125

Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys
130 135 140

Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly
145 150 155 160

Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro
165 170 175

Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu
180 185 190

Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu
195 200 205

His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro
210 215 220

Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu Arg Val
225 230 235 240

Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu
245 250 255

Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln Val
260 265 270

Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu
275 280 285

Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln
290 295 300

Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr
305 310 315 320

Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro
325 330 335

Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro
340 345 350

Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly
355 360 365

Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr
370 375 380

Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn
385 390 395 400

Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg
405 410 415

Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val
420 425 430

Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu
435 440 445

Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Ile
450 455 460

Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala
465 470 475 480

Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly
485 490 495

Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro
500 505 510

Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro
515 520 525

Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser
530 535 540

Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu
545 550 555 560

Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser
565 570 575

Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro Pro Gln
580 585 590

Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn Ser Arg
595 600 605

Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly
610 615 620

Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg
625 630 635 640

Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser Gln Phe
645 650 655

Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln
660 665 670

Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg
675 680 685

Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn
690 695 700

Thr Gln Gln Val Asn
705

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ccctcgtccc gcgcccccgg ggctcgcgga gccaggtctc cacctctggg caggagagtt 120

gccgaccacc tcgggggtgc tttctctgcg cttgaacatc tatagctgct tctgaggggc 180

tgggagccgg gcccctggga gagacgagcc atgaaccccc cacagcctct gcatttgggg 240

acctcacctt aggagagtgc catttacagc ttccgccagg gcaaaggagc tgagcagcca 300

tcccaagccc agcccacctc cctcccccgg cccctggtag gcatggacta gcagctgtga 360

gcagccagag ctg atg ccc ggc ccc cag ggg ggc aga ggc gcc gcc acc 409
Met Pro Gly Pro Gln Gly Gly Arg Gly Ala Ala Thr
1 5 10

atg agc ctg ggc aag ctc tcg cct gtg ggc tgg gtg tcc agt tca cag 457
Met Ser Leu Gly Lys Leu Ser Pro Val Gly Trp Val Ser Ser Ser Gln
15 20 25

gga aag agg cgg ctg act gca gac atg atc agc cac cca ctc ggg gac 505
Gly Lys Arg Arg Leu Thr Ala Asp Met Ile Ser His Pro Leu Gly Asp
30 35 40

ttc cgc cac acc atg cat gtg ggc cgt ggc ggg gat gtc ttc ggg gac 553
Phe Arg His Thr Met His Val Gly Arg Gly Gly Asp Val Phe Gly Asp
45 50 55 60

acg tcc ttc ctc agc aac cac ggt ggc agc tcc ggg agc acc cat cgc 601
Thr Ser Phe Leu Ser Asn His Gly Gly Ser Ser Gly Ser Thr His Arg
65 70 75

tca ccc cgc agc ttc ctg gcc aag aag ctg cag ctg gtg cgg agg gtg 649
Ser Pro Arg Ser Phe Leu Ala Lys Lys Leu Gln Leu Val Arg Arg Val
80 85 90

ggg gcg ccc ccc cgg agg atg gca tct ccc cct gca ccc tcc ccg gct 697

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Gly Ala Pro Pro Arg Arg Met Ala Ser Pro Pro Ala Pro Ser Pro Ala
        95                  100                 105

cca ccg gcc atc tcc ccc atc atc aag aac gcc atc tcc ctg ccc cag      745
Pro Pro Ala Ile Ser Pro Ile Ile Lys Asn Ala Ile Ser Leu Pro Gln
    110                 115                 120

ctc aac cag gcc gcc tac gac agc ctc gtg gtt ggc aag ctc agc ttc      793
Leu Asn Gln Ala Ala Tyr Asp Ser Leu Val Val Gly Lys Leu Ser Phe
125                 130                 135                 140

gac agc agc ccc acc agc tcc acg gac ggc cac tcc agc tac ggc ctg      841
Asp Ser Ser Pro Thr Ser Ser Thr Asp Gly His Ser Ser Tyr Gly Leu
                145                 150                 155

gac tct ggg ttc tgc acc atc tcc cgc ctg ccc cgc tcg gaa aag ccg      889
Asp Ser Gly Phe Cys Thr Ile Ser Arg Leu Pro Arg Ser Glu Lys Pro
            160                 165                 170

cat gac cga gac cgg gat ggt tcc ttc ccc tct gag ccc ggg ctt cgc      937
His Asp Arg Asp Arg Asp Gly Ser Phe Pro Ser Glu Pro Gly Leu Arg
        175                 180                 185

cgc tct gac tct ctc ttg tcc ttc cgc ctg gac ctc gac ctt ggg ccc      985
Arg Ser Asp Ser Leu Leu Ser Phe Arg Leu Asp Leu Asp Leu Gly Pro
    190                 195                 200

tca ctc ctc agc gag ctg cta ggg gtc atg agc ctc cca gaa gcc cct     1033
Ser Leu Leu Ser Glu Leu Leu Gly Val Met Ser Leu Pro Glu Ala Pro
205                 210                 215                 220

gca gct gag act cca gcc ccc gct gca aac ccc cca gcc cct act gca     1081
Ala Ala Glu Thr Pro Ala Pro Ala Ala Asn Pro Pro Ala Pro Thr Ala
                225                 230                 235

aac ccc acg ggt cct gct gca aac ccc cca gcg cct gct gca aac ccc     1129
Asn Pro Thr Gly Pro Ala Ala Asn Pro Pro Ala Pro Ala Ala Asn Pro
            240                 245                 250

tca gca cct gcc gca acc ccc acg ggt cct gct gca aat ccc cca gcc     1177
Ser Ala Pro Ala Ala Thr Pro Thr Gly Pro Ala Ala Asn Pro Pro Ala
        255                 260                 265

cct gcc gca agc tcc aca ccc cat gga cac tgt ccc aat ggg gta aca     1225
Pro Ala Ala Ser Ser Thr Pro His Gly His Cys Pro Asn Gly Val Thr
    270                 275                 280

gct ggg ttg ggc cca gtg gct gag gtg aag tcc agc cca gtg gga ggg     1273
Ala Gly Leu Gly Pro Val Ala Glu Val Lys Ser Ser Pro Val Gly Gly
285                 290                 295                 300

ggt ccc cga gga cct gct ggc cct gcc ctc ggc agg cac tgg gga gca     1321
Gly Pro Arg Gly Pro Ala Gly Pro Ala Leu Gly Arg His Trp Gly Ala
                305                 310                 315

ggc tgg gat ggc ggc cac cac tac cca gag atg gat gcg cgg cag gag     1369
Gly Trp Asp Gly Gly His His Tyr Pro Glu Met Asp Ala Arg Gln Glu
            320                 325                 330

cgg gtg gag gtg ctg ccc caa gcc cgg gcc tcc tgg gag agc ctg gac     1417
Arg Val Glu Val Leu Pro Gln Ala Arg Ala Ser Trp Glu Ser Leu Asp
        335                 340                 345

gaa gag tgg agg gcg ccc cag gca ggc agc agg acc cca gtg ccc agc     1465
Glu Glu Trp Arg Ala Pro Gln Ala Gly Ser Arg Thr Pro Val Pro Ser
    350                 355                 360

aca gtg caa gca aac acc ttt gaa ttt gcg gat gct gag gag gat gat     1513
Thr Val Gln Ala Asn Thr Phe Glu Phe Ala Asp Ala Glu Glu Asp Asp
365                 370                 375                 380

gag gtc aag gtg tga ggggctgggg cacggtccca gggccccacc taggtgcaga     1568
Glu Val Lys Val

gccggcccct cacctaacag ctggttccta ccagaccgga gaggggagaa gtcatgttgc   1628

ccctaaaccc ctccccacct ctgcaggaca gacatgggag ggaggacagg gaaggccagg   1688

cttgctctgg gacttttatg ctcccagagg ccctgccaaa ctgaccacct cccccgactg   1748
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ccactctgga cctaatagct gttccttagg ccccactcca tgccaccccc accagctgga 1808
ggacccagcc tcacagtgtg tcctttgtgc cagaccaagc ggcccgtggg gggtgggggg 1868
cagggagtgt accacacagg gccattgtct cacctcccaa agggaccgcc tgcccccagc 1928
tcatcccaga gcgtccctgc tgcaaccctg acagccgtct cccaggccgc ttccccaaca 1988
tccccgcccc agcctccctc ttaccccaga aaggtcaggt atgacctccc ggggaggaat 2048
cccacctgcc tgtatacccc agacttgcct ctggggcctg attaaataag gctgttttga 2108
taaaaaaaaa aaaaaaaaaa aaa 2131

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<400> 56

Met Pro Gly Pro Gln Gly Gly Arg Gly Ala Ala Thr Met Ser Leu Gly
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Lys Leu Ser Pro Val Gly Trp Val Ser Ser Ser Gln Gly Lys Arg Arg
20 25 30

Leu Thr Ala Asp Met Ile Ser His Pro Leu Gly Asp Phe Arg His Thr
35 40 45

Met His Val Gly Arg Gly Gly Asp Val Phe Gly Asp Thr Ser Phe Leu
50 55 60

Ser Asn His Gly Gly Ser Ser Gly Ser Thr His Arg Ser Pro Arg Ser
65 70 75 80

Phe Leu Ala Lys Lys Leu Gln Leu Val Arg Arg Val Gly Ala Pro Pro
85 90 95

Arg Arg Met Ala Ser Pro Pro Ala Pro Ser Pro Ala Pro Pro Ala Ile
100 105 110

Ser Pro Ile Ile Lys Asn Ala Ile Ser Leu Pro Gln Leu Asn Gln Ala
115 120 125

Ala Tyr Asp Ser Leu Val Val Gly Lys Leu Ser Phe Asp Ser Ser Pro
130 135 140

Thr Ser Ser Thr Asp Gly His Ser Ser Tyr Gly Leu Asp Ser Gly Phe
145 150 155 160

Cys Thr Ile Ser Arg Leu Pro Arg Ser Glu Lys Pro His Asp Arg Asp
165 170 175

Arg Asp Gly Ser Phe Pro Ser Glu Pro Gly Leu Arg Arg Ser Asp Ser
180 185 190

Leu Leu Ser Phe Arg Leu Asp Leu Asp Leu Gly Pro Ser Leu Leu Ser
195 200 205

Glu Leu Leu Gly Val Met Ser Leu Pro Glu Ala Pro Ala Ala Glu Thr
210 215 220

Pro Ala Pro Ala Ala Asn Pro Pro Ala Pro Thr Ala Asn Pro Thr Gly
225 230 235 240

Pro Ala Ala Asn Pro Pro Ala Pro Ala Ala Asn Pro Ser Ala Pro Ala
245 250 255

Ala Thr Pro Thr Gly Pro Ala Ala Asn Pro Pro Ala Pro Ala Ala Ser
260 265 270

Ser Thr Pro His Gly His Cys Pro Asn Gly Val Thr Ala Gly Leu Gly
275 280 285

Pro Val Ala Glu Val Lys Ser Ser Pro Val Gly Gly Gly Pro Arg Gly
290 295 300

Pro Ala Gly Pro Ala Leu Gly Arg His Trp Gly Ala Gly Trp Asp Gly
305 310 315 320

Gly His His Tyr Pro Glu Met Asp Ala Arg Gln Glu Arg Val Glu Val
325 330 335

Leu Pro Gln Ala Arg Ala Ser Trp Glu Ser Leu Asp Glu Glu Trp Arg
340 345 350

Ala Pro Gln Ala Gly Ser Arg Thr Pro Val Pro Ser Thr Val Gln Ala
355 360 365

Asn Thr Phe Glu Phe Ala Asp Ala Glu Glu Asp Asp Glu Val Lys Val
370 375 380

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ctacgtgata gtaaatcccc ggcaaaaacc agcagcgcct tgcaagccca cgccacccca 180

agcatcccag gactcttctg aaacgactcc gggctaccag atcggccgtc cagctggaat 240

caaccg atg gag gct ccg ctg caa act gga atg gtg ctt ggc gtg atg 288
Met Glu Ala Pro Leu Gln Thr Gly Met Val Leu Gly Val Met
1 5 10

atc ggg gcc gga gtg gcg gtg gtg gtc acg gcc gtg ctc atc ctc ctg 336
Ile Gly Ala Gly Val Ala Val Val Val Thr Ala Val Leu Ile Leu Leu
15 20 25 30

gtg gtg cgg agg ctg cga gtg cca aaa acc cca gcc ccg gat ggc ccc 384
Val Val Arg Arg Leu Arg Val Pro Lys Thr Pro Ala Pro Asp Gly Pro
35 40 45

cgg tat cgg ttc cgg aag agg gac aaa gtg ctc ttc tat ggc cgg aag 432
Arg Tyr Arg Phe Arg Lys Arg Asp Lys Val Leu Phe Tyr Gly Arg Lys
50 55 60

att atg cgg aag gtg tca caa tcc acc tcc tcc ctc gtg gat acc tct 480
Ile Met Arg Lys Val Ser Gln Ser Thr Ser Ser Leu Val Asp Thr Ser
65 70 75

gtc tcc gcc acc tcc cgg cca cgc atg agg aag aaa ctg aag atg ctc 528
Val Ser Ala Thr Ser Arg Pro Arg Met Arg Lys Lys Leu Lys Met Leu
80 85 90

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aac att gcc aag aag atc ctg cgc atc cag aaa gag acg ccc acg ctg      576
Asn Ile Ala Lys Lys Ile Leu Arg Ile Gln Lys Glu Thr Pro Thr Leu
95                  100                 105                 110

cag cgg aag gag ccc ccg ccc gca gtg cta gaa gct gac ctg acc gag      624
Gln Arg Lys Glu Pro Pro Pro Ala Val Leu Glu Ala Asp Leu Thr Glu
                115                 120                 125

ggc gac ctg gct aac tcc cat ctg ccc tct gaa gtg ctt tat atg ctc      672
Gly Asp Leu Ala Asn Ser His Leu Pro Ser Glu Val Leu Tyr Met Leu
            130                 135                 140

aag aac gtc cgg gtg ctg ggc cac ttc gag aag cca ctc ttc ctg gag      720
Lys Asn Val Arg Val Leu Gly His Phe Glu Lys Pro Leu Phe Leu Glu
        145                 150                 155

ctc tgc cgc cac atg gtc ttc cag cgg ctg ggc cag ggt gac tac gtc      768
Leu Cys Arg His Met Val Phe Gln Arg Leu Gly Gln Gly Asp Tyr Val
    160                 165                 170

ttc cgg ccg ggc cag cca gat gcc agc atc tac gtg gtg cag gac ggg      816
Phe Arg Pro Gly Gln Pro Asp Ala Ser Ile Tyr Val Val Gln Asp Gly
175                 180                 185                 190

ctg ctg gag ctc tgt ctg cca ggg cct gac ggg aag gag tgt gtg gtg      864
Leu Leu Glu Leu Cys Leu Pro Gly Pro Asp Gly Lys Glu Cys Val Val
                195                 200                 205

aag gaa gtg gtt cct ggg gac agc gtc aac agc ctt ctc agc atc ctg      912
Lys Glu Val Val Pro Gly Asp Ser Val Asn Ser Leu Leu Ser Ile Leu
            210                 215                 220

gat gtc atc acc ggt cac cag cat ccc cag cgg acc gtg tct gcc cgg      960
Asp Val Ile Thr Gly His Gln His Pro Gln Arg Thr Val Ser Ala Arg
        225                 230                 235

gcg gcc cgg gac tcc acg gtg ctg cgc ctg ccg gtg gaa gca ttc tcc     1008
Ala Ala Arg Asp Ser Thr Val Leu Arg Leu Pro Val Glu Ala Phe Ser
    240                 245                 250

gcg gtc ttc acc aag tac ccg gag agc ttg gtg cgg gtc gtg cag atc     1056
Ala Val Phe Thr Lys Tyr Pro Glu Ser Leu Val Arg Val Val Gln Ile
255                 260                 265                 270

atc atg gtg cgg ctg cag cga gtc acc ttc ctg gca ctg cac aac tac     1104
Ile Met Val Arg Leu Gln Arg Val Thr Phe Leu Ala Leu His Asn Tyr
                275                 280                 285

ctg ggt ctg acc aat gag ctc ttc agc cac gag atc cag ccc ctg cgt     1152
Leu Gly Leu Thr Asn Glu Leu Phe Ser His Glu Ile Gln Pro Leu Arg
            290                 295                 300

ctg ttc ccc agc ccc ggc ctc cca act cgc acc agc cct gtg cgg ggc     1200
Leu Phe Pro Ser Pro Gly Leu Pro Thr Arg Thr Ser Pro Val Arg Gly
        305                 310                 315

tcc aag aga atg gtc agc acc tca gct aca gac gag ccc agg gag acc     1248
Ser Lys Arg Met Val Ser Thr Ser Ala Thr Asp Glu Pro Arg Glu Thr
    320                 325                 330

cca ggg cgg cca ccc gat ccc acc ggg gcc ccg ctg cct gga cct aca     1296
Pro Gly Arg Pro Pro Asp Pro Thr Gly Ala Pro Leu Pro Gly Pro Thr
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ggg gac cct gtg aag ccc aca tcc ctg gaa acc ccc tcg ccc cct ctg     1344
Gly Asp Pro Val Lys Pro Thr Ser Leu Glu Thr Pro Ser Pro Pro Leu
                355                 360                 365

ctg agc cgc tgc gtc tcc atg cca ggg gac atc tca ggc ttg cag ggt     1392
Leu Ser Arg Cys Val Ser Met Pro Gly Asp Ile Ser Gly Leu Gln Gly
            370                 375                 380

ggc ccc cgc tcc gac ttc gac atg gcc tat gag cgt ggc cgg atc tcc     1440
Gly Pro Arg Ser Asp Phe Asp Met Ala Tyr Glu Arg Gly Arg Ile Ser
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gtg tcc ctg caa gaa gag gcc tcc ggg ggg tcc ctg gca gcc ccc gct     1488
Val Ser Leu Gln Glu Glu Ala Ser Gly Gly Ser Leu Ala Ala Pro Ala
    400                 405                 410
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cgg acc ccc act cag gag cct cgt gag cag ccg gca ggc gcc tgt gaa      1536
Arg Thr Pro Thr Gln Glu Pro Arg Glu Gln Pro Ala Gly Ala Cys Glu
415                 420                 425                 430

tac agc tac tgt gag gat gag tcg gcc act ggt ggc tgc cct ttc ggg      1584
Tyr Ser Tyr Cys Glu Asp Glu Ser Ala Thr Gly Gly Cys Pro Phe Gly
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ccc tac cag ggc cgc cag acc agc agc atc ttc gag gca gca aag cag      1632
Pro Tyr Gln Gly Arg Gln Thr Ser Ser Ile Phe Glu Ala Ala Lys Gln
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gag ctg gcc aag ctg atg cgg att gag gac ccc tcc ctc ctg aac agc      1680
Glu Leu Ala Lys Leu Met Arg Ile Glu Asp Pro Ser Leu Leu Asn Ser
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aga gtc ttg ctg cac cac gcc aaa gct ggc acc atc att gcc cgc cag      1728
Arg Val Leu Leu His His Ala Lys Ala Gly Thr Ile Ile Ala Arg Gln
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Gly Asp Gln Asp Val Ser Leu His Phe Val Leu Trp Gly Cys Leu His
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gtg tac cag cgc atg atc gac aag gcg gag gac gtg tgc ctg ttc gta      1824
Val Tyr Gln Arg Met Ile Asp Lys Ala Glu Asp Val Cys Leu Phe Val
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gcg cag ccc ggg gaa ctg gtg ggg cag ctg gcg gtg ctc act ggc gaa      1872
Ala Gln Pro Gly Glu Leu Val Gly Gln Leu Ala Val Leu Thr Gly Glu
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cct ctc atc ttc aca ctg cga gcc caa cgc gac tgc acc ttc ctg cgg      1920
Pro Leu Ile Phe Thr Leu Arg Ala Gln Arg Asp Cys Thr Phe Leu Arg
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atc tcc aag tcc gac ttc tat gag atc atg cgc gca cag ccc agt gtg      1968
Ile Ser Lys Ser Asp Phe Tyr Glu Ile Met Arg Ala Gln Pro Ser Val
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gtg ctg agt gcg gcg cac acg gtg gca gcc agg atg tcg ccc ttc gtg      2016
Val Leu Ser Ala Ala His Thr Val Ala Ala Arg Met Ser Pro Phe Val
575                 580                 585                 590

cgc cag atg gac ttc gcc atc gac tgg act gca gtg gag gcg gga cgc      2064
Arg Gln Met Asp Phe Ala Ile Asp Trp Thr Ala Val Glu Ala Gly Arg
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gcg ctg tac agg cag ggc gac cgc tcc gac tgc act tac atc gtg ctc      2112
Ala Leu Tyr Arg Gln Gly Asp Arg Ser Asp Cys Thr Tyr Ile Val Leu
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aat ggg cgg ctg cgt agc gtg atc cag cga ggc agt ggc aag aag gag      2160
Asn Gly Arg Leu Arg Ser Val Ile Gln Arg Gly Ser Gly Lys Lys Glu
        625                 630                 635

ctg gtg ggc gag tac ggc cgc ggc gac ctc atc ggc gtg gtg gag gca      2208
Leu Val Gly Glu Tyr Gly Arg Gly Asp Leu Ile Gly Val Val Glu Ala
    640                 645                 650

ctg acc cgg cag ccg cga gcc acg acg gtg cac gcg gtg cgc gac acg      2256
Leu Thr Arg Gln Pro Arg Ala Thr Thr Val His Ala Val Arg Asp Thr
655                 660                 665                 670

gag ctg gcc aag ctt ccc gag ggc acc ttg ggt cac atc aaa cgc cgg      2304
Glu Leu Ala Lys Leu Pro Glu Gly Thr Leu Gly His Ile Lys Arg Arg
                675                 680                 685

tac ccg cag gtc gtg acc cgc ctt atc cac cta ctg agc cag aaa att      2352
Tyr Pro Gln Val Val Thr Arg Leu Ile His Leu Leu Ser Gln Lys Ile
            690                 695                 700

cta ggg aat ttg cag cag ctg caa gga ccc ttc cca gca ggc tct ggg      2400
Leu Gly Asn Leu Gln Gln Leu Gln Gly Pro Phe Pro Ala Gly Ser Gly
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ttg ggt gtg ccc cca cac tcg gaa ctc acc aac cca gcc agc aac ctg      2448
Leu Gly Val Pro Pro His Ser Glu Leu Thr Asn Pro Ala Ser Asn Leu
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Phe Thr Leu Glu Leu Gln His Ala Leu Gln Ala Ile Gly Pro Thr Leu
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ctc ctt aac agt gac atc atc cgg gca cgc ctg ggg gcc tcc gca ctg      2592
Leu Leu Asn Ser Asp Ile Ile Arg Ala Arg Leu Gly Ala Ser Ala Leu
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gat agc atc caa gag ttc cgg ctg tca ggg tgg ctg gcc cag cag gag      2640
Asp Ser Ile Gln Glu Phe Arg Leu Ser Gly Trp Leu Ala Gln Gln Glu
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gat gca cac cgt atc gta ctc tac cag acg gac gcc tcg ctg acg ccc      2688
Asp Ala His Arg Ile Val Leu Tyr Gln Thr Asp Ala Ser Leu Thr Pro
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tgg acc gtg cgc tgc ctg cga cag gcc gac tgc atc ctc att gtg ggc      2736
Trp Thr Val Arg Cys Leu Arg Gln Ala Asp Cys Ile Leu Ile Val Gly
815                 820                 825                 830

ctg ggg gac cag gag cct acc ctc ggc cag ctg gag cag atg ctg gag      2784
Leu Gly Asp Gln Glu Pro Thr Leu Gly Gln Leu Glu Gln Met Leu Glu
                835                 840                 845

aac acg gct gtg cgc gcc ctt aag cag cta gtc ctg ctc cac cga gag      2832
Asn Thr Ala Val Arg Ala Leu Lys Gln Leu Val Leu Leu His Arg Glu
            850                 855                 860

gag ggc gcg ggc ccc acg cgc acc gtg gag tgg cta aat atg cgc agc      2880
Glu Gly Ala Gly Pro Thr Arg Thr Val Glu Trp Leu Asn Met Arg Ser
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Trp Cys Ser Gly His Leu His Leu Arg Cys Pro Arg Arg Leu Phe Ser
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cgc cgc agc cct gcc aag ctg cat gag ctc tac gag aag gtt ttc tcc      2976
Arg Arg Ser Pro Ala Lys Leu His Glu Leu Tyr Glu Lys Val Phe Ser
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agg cgc gcg gac cgg cac agc gac ttc tcc cgc ttg gcg agg gtg ctc      3024
Arg Arg Ala Asp Arg His Ser Asp Phe Ser Arg Leu Ala Arg Val Leu
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acg ggg aac acc att gcc ctt gtg cta ggc ggg ggc ggg gcc agg ggc      3072
Thr Gly Asn Thr Ile Ala Leu Val Leu Gly Gly Gly Gly Ala Arg Gly
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tgc tcg cac atc gga gta cta aag gca tta gag gag gcg ggg gtc ccc      3120
Cys Ser His Ile Gly Val Leu Lys Ala Leu Glu Glu Ala Gly Val Pro
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Val Asp Leu Val Gly Gly Thr Ser Ile Gly Ser Phe Ile Gly Ala Leu
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tac gcg gag gag cgc agc gcc agc cgc acg agg cag cgg gcc cgg gag      3216
Tyr Ala Glu Glu Arg Ser Ala Ser Arg Thr Arg Gln Arg Ala Arg Glu
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tgg gcc aag agc atg act tcg gtg ctg gaa  cct gtg ttg gac ctc  acg    3264
Trp Ala Lys Ser Met Thr Ser Val Leu Glu  Pro Val Leu Asp Leu  Thr
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tac cca gtc acc  tcc atg ttc act ggg  tct gcc ttt aac cgc  agc      3309
Tyr Pro Val Thr  Ser Met Phe Thr Gly  Ser Ala Phe Asn Arg  Ser
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atc cat cgg gtc  ttc cag gat aag cag  att gag gac ctg tgg  ctg      3354
Ile His Arg Val  Phe Gln Asp Lys Gln  Ile Glu Asp Leu Trp  Leu
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cct tac ttc aac  gtg acc aca gat atc  acc gcc tca gcc atg  cga      3399
Pro Tyr Phe Asn  Val Thr Thr Asp Ile  Thr Ala Ser Ala Met  Arg
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Thr Leu Ser Gly Tyr Leu Pro Pro Leu Cys Asp Pro Lys Asp Gly
1070 1075 1080

cac cta ctc atg gat ggc ggc tac atc aac aat ctg cca gcg gac 3534
His Leu Leu Met Asp Gly Gly Tyr Ile Asn Asn Leu Pro Ala Asp
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Ile Ala Arg Ser Met Gly Ala Lys Thr Val Ile Ala Ile Asp Val
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Lys Met Leu Thr Asp Arg Arg Ser Thr Asp Leu Asn Glu Ser Arg
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cgt gca gac gtg ctt gcc ttc cca agc tct ggc ttc act gac ttg 3984
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gca gag att gtg tcc cgg att gag ccc ccc acg agc tat gtc tct 4029
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ccc gag ggc gca agc ccc agc act gcc tcc gag atg gag gag gag 4164
Pro Glu Gly Ala Ser Pro Ser Thr Ala Ser Glu Met Glu Glu Glu
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Arg Phe Arg Lys Arg Asp Lys Val Leu Phe Tyr Gly Arg Lys Ile Met
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Ala Thr Ser Arg Pro Arg Met Arg Lys Lys Leu Lys Met Leu Asn Ile
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Val Arg Val Leu Gly His Phe Glu Lys Pro Leu Phe Leu Glu Leu Cys
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Phe Thr Lys Tyr Pro Glu Ser Leu Val Arg Val Val Gln Ile Ile Met
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Lys Ser Asp Phe Tyr Glu Ile Met Arg Ala Gln Pro Ser Val Val Leu
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His Ile Gly Val Leu Lys Ala Leu Glu Glu Ala Gly Val Pro Val Asp
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Ile Phe Leu Gln Ser Leu Leu Gly Phe Gly Thr Lys Ala Val Leu Ala
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Gly Pro Gly Cys Ser Leu Met Pro Pro Pro Pro Gln Glu Cys Ala Gly
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Glu Pro Leu Phe Met Leu Tyr Cys Ala Ile Lys Gln Gln Met Glu Lys
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Asp Lys Leu Ile Arg Gln Gln Ile Asp Tyr Lys Thr Leu Thr Leu Asn
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Cys Val Asn Pro Glu Asn Glu Asn Ala Pro Glu Val Pro Val Lys Gly
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            140                 145                 150

gcc tac aag ggc gtg ccc tac tcc cag cgg ccc aag gcc gcg gac atg      1854
Ala Tyr Lys Gly Val Pro Tyr Ser Gln Arg Pro Lys Ala Ala Asp Met
        155                 160                 165

gac ctg gag tgg cgc cag ggc cgc atg gcg cgc atc atc ctg cag gac      1902
Asp Leu Glu Trp Arg Gln Gly Arg Met Ala Arg Ile Ile Leu Gln Asp
    170                 175                 180

gag gac gtc acc acc aag att gac aac gat tgg aag agg ctg aac aca      1950
Glu Asp Val Thr Thr Lys Ile Asp Asn Asp Trp Lys Arg Leu Asn Thr
185                 190                 195                 200

ctg gct cac tac cag gtg aca gac ggg tcc tcg gtg gca ctg gtg ccc      1998
Leu Ala His Tyr Gln Val Thr Asp Gly Ser Ser Val Ala Leu Val Pro
                205                 210                 215

aag cag acg tcc gcc tac aac atc tcc aac tcc tcc acc ttc acc aag      2046
Lys Gln Thr Ser Ala Tyr Asn Ile Ser Asn Ser Ser Thr Phe Thr Lys
            220                 225                 230

tcc ctc agc aga tac gag agc atg ctg cgc acg gcc agc agc ccc gac      2094
Ser Leu Ser Arg Tyr Glu Ser Met Leu Arg Thr Ala Ser Ser Pro Asp
        235                 240                 245

agc ctg cgc tcg cgc acg ccc atg atc acg ccc gac ctg gag agc ggc      2142
Ser Leu Arg Ser Arg Thr Pro Met Ile Thr Pro Asp Leu Glu Ser Gly
    250                 255                 260

acc aag ctg tgg cac ctg gtg aag aac cac gac cac ctg gac cag cgt      2190
Thr Lys Leu Trp His Leu Val Lys Asn His Asp His Leu Asp Gln Arg
265                 270                 275                 280

gag ggt gac cgc ggc agc aag atg gtc tcg gag atc tac ttg aca cgg      2238
Glu Gly Asp Arg Gly Ser Lys Met Val Ser Glu Ile Tyr Leu Thr Arg
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                285                 290                 295

cta ctg gcc acc aag ggc aca ctg cag aag ttt gtg gac gac ctg ttt      2286
Leu Leu Ala Thr Lys Gly Thr Leu Gln Lys Phe Val Asp Asp Leu Phe
            300                 305                 310

gag acc atc ttc agc acg gca cac cgg ggc tca gcc ctg ccg ctg gcc      2334
Glu Thr Ile Phe Ser Thr Ala His Arg Gly Ser Ala Leu Pro Leu Ala
        315                 320                 325

atc aag tac atg ttc gac ttc ctg gat gag cag gcc gac aag cac cag      2382
Ile Lys Tyr Met Phe Asp Phe Leu Asp Glu Gln Ala Asp Lys His Gln
    330                 335                 340

atc cac gat gct gac gtg cgc cac acc tgg aag agc aac tgc ctg ccc      2430
Ile His Asp Ala Asp Val Arg His Thr Trp Lys Ser Asn Cys Leu Pro
345                 350                 355                 360

ctg cgc ttc tgg gtg aac gtg atc aag aac cca cag ttt gtg ttc gac      2478
Leu Arg Phe Trp Val Asn Val Ile Lys Asn Pro Gln Phe Val Phe Asp
                365                 370                 375

att cac aag aac agc acc acg gac gcc tgc ttg tcg gtg gtg gcc cag      2526
Ile His Lys Asn Ser Thr Thr Asp Ala Cys Leu Ser Val Val Ala Gln
            380                 385                 390

acc ttc atg gac tcc tgc tcc acc tct gag cac aag ctg ggc aag gac      2574
Thr Phe Met Asp Ser Cys Ser Thr Ser Glu His Lys Leu Gly Lys Asp
        395                 400                 405

tca ccc tcc aac aag ctg ctc tac gcc aag gac atc ccc aac tac aag      2622
Ser Pro Ser Asn Lys Leu Leu Tyr Ala Lys Asp Ile Pro Asn Tyr Lys
    410                 415                 420

agc tgg gtg gag agg tac tat gca gac atc gcc aag atg cca gcc atc      2670
Ser Trp Val Glu Arg Tyr Tyr Ala Asp Ile Ala Lys Met Pro Ala Ile
425                 430                 435                 440

agc gac cag gac atg agt gcg tat ctg gct gag cag tcc cgc ctg cac      2718
Ser Asp Gln Asp Met Ser Ala Tyr Leu Ala Glu Gln Ser Arg Leu His
                445                 450                 455

ctg agc cag ttc aac agc atg agc gcc ttg cac gag atc tac tcc tac      2766
Leu Ser Gln Phe Asn Ser Met Ser Ala Leu His Glu Ile Tyr Ser Tyr
            460                 465                 470

atc acc aag tac aag gat gag atc ctg gca gcc ctg gag aag gat gag      2814
Ile Thr Lys Tyr Lys Asp Glu Ile Leu Ala Ala Leu Glu Lys Asp Glu
        475                 480                 485

cag gcg cgg cgg cag cgg ctg cgg agc aag ctg gag cag gtg gtg gac      2862
Gln Ala Arg Arg Gln Arg Leu Arg Ser Lys Leu Glu Gln Val Val Asp
    490                 495                 500

acg atg gcc ctg agc agc tga gccccagctg tgatcatcca gcatgatgca        2913
Thr Met Ala Leu Ser Ser
505                 510

gcgtgaggac agctgagcag ggaccgggac agccctcacc gcatgcgtgt ggagtgtccg   2973

gtggtgctcg ggccgccgca gtgcagcgac tgcccggccc tccctccccc gcctcacccg   3033

gtcgggtccc ggctcttcct gtgtggaggt gatggtacct gccacaccac agctgcgcac   3093

acagctgctt gctcaggggc cgggacagca ctgggtgctc aggctggcca aggaccttca   3153

ttgcctggca agagctgccc agtggccttc atgggagaag ggctgacctc tgaggggctg   3213

aggggtgagg ccagggccct ccaggggggag gggtagccag cttgggctgt ccccttgaga   3273

ccaggacaag aggctggggg tgtcagcatt cccagctttc caagctgccc ccaggcggca   3333

gagtctgagg gtcccggggc ccggttggca gctggagaaa gaggcaaaaa gcccgtagcc   3393

gggcaagagg agctcaagtc ggtctgggcc cgttgccacc gactcccacc tccagcaccc   3453

atgcccgctg caccgctgcc atcctcagat tcaccgcgtg ctctgcgcgg ccgaggccgg   3513

agcaccacat ccacctcgcc ccagagaggc tctgctccct cctatggagg ggctgtgggc   3573
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caggctgctc agactcctgg gtggcttcca gacggaccgg gcagcccctc tccgtcctca 3633
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gccatgagtg acgggcagtg accagaggga ctggaggcca gcggtgtcca cccttgccct 4053
cagcaagaga gaatgcattc ttaaaagaaa gctgtacatg tatatatatg catatatata 4113
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aattttaaag acgatttgaa caagaaaatg aaggcagtgg gaaagcaatg ccaaatggtt 4233
gtggagaaag tggccggagc ctccctggag tggagcagcc ctgaagcctg tgccccccga 4293
cctgcgggcc gctgttttgg tttgacatga caaggaaagg acttcctgct gaccctgaga 4353
gcctctgggg tgccgcggca ccacggggca tgcatgattg tgctagcgtt tagtctgagt 4413
tgatcttttt aaaactgcaa gtgttgaata ct 4445

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<211> 510
<212> PRT
<213> Homo sapiens

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Met Val Gly Met Phe Cys Phe Leu Ile Phe Leu Gln Ser Leu Leu Gly
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Phe Gly Thr Lys Ala Val Leu Ala Ser Gln Arg Val Gly Lys Cys Cys
20 25 30

Ser Phe Leu Leu Ala Arg Asn Thr Met Ala Gly Thr Arg Arg Val Glu
35 40 45

Gly Gln Val Gly Gly Arg Pro Gly Gly Pro Gly Cys Ser Leu Met Pro
50 55 60

Pro Pro Pro Gln Glu Cys Ala Gly Glu Pro Leu Phe Met Leu Tyr Cys
65 70 75 80

Ala Ile Lys Gln Gln Met Glu Lys Gly Pro Ile Asp Ala Ile Thr Gly
85 90 95

Glu Ala Arg Tyr Ser Leu Ser Glu Asp Lys Leu Ile Arg Gln Gln Ile
100 105 110

Asp Tyr Lys Thr Leu Thr Leu Asn Cys Val Asn Pro Glu Asn Glu Asn
115 120 125

Ala Pro Glu Val Pro Val Lys Gly Leu Asp Cys Asp Thr Val Thr Gln
130 135 140

Ala Lys Glu Lys Leu Leu Asp Ala Ala Tyr Lys Gly Val Pro Tyr Ser
145 150 155 160

Gln Arg Pro Lys Ala Ala Asp Met Asp Leu Glu Trp Arg Gln Gly Arg
165 170 175

Met Ala Arg Ile Ile Leu Gln Asp Glu Asp Val Thr Thr Lys Ile Asp
180 185 190

Asn Asp Trp Lys Arg Leu Asn Thr Leu Ala His Tyr Gln Val Thr Asp
195 200 205

Gly Ser Ser Val Ala Leu Val Pro Lys Gln Thr Ser Ala Tyr Asn Ile
210 215 220

Ser Asn Ser Ser Thr Phe Thr Lys Ser Leu Ser Arg Tyr Glu Ser Met
225 230 235 240

Leu Arg Thr Ala Ser Ser Pro Asp Ser Leu Arg Ser Arg Thr Pro Met
245 250 255

Ile Thr Pro Asp Leu Glu Ser Gly Thr Lys Leu Trp His Leu Val Lys
260 265 270

Asn His Asp His Leu Asp Gln Arg Glu Gly Asp Arg Gly Ser Lys Met
275 280 285

Val Ser Glu Ile Tyr Leu Thr Arg Leu Leu Ala Thr Lys Gly Thr Leu
290 295 300

Gln Lys Phe Val Asp Asp Leu Phe Glu Thr Ile Phe Ser Thr Ala His
305 310 315 320

Arg Gly Ser Ala Leu Pro Leu Ala Ile Lys Tyr Met Phe Asp Phe Leu
325 330 335

Asp Glu Gln Ala Asp Lys His Gln Ile His Asp Ala Asp Val Arg His
340 345 350

Thr Trp Lys Ser Asn Cys Leu Pro Leu Arg Phe Trp Val Asn Val Ile
355 360 365

Lys Asn Pro Gln Phe Val Phe Asp Ile His Lys Asn Ser Thr Thr Asp
370 375 380

Ala Cys Leu Ser Val Val Ala Gln Thr Phe Met Asp Ser Cys Ser Thr
385 390 395 400

Ser Glu His Lys Leu Gly Lys Asp Ser Pro Ser Asn Lys Leu Leu Tyr
405 410 415

Ala Lys Asp Ile Pro Asn Tyr Lys Ser Trp Val Glu Arg Tyr Tyr Ala
420 425 430

Asp Ile Ala Lys Met Pro Ala Ile Ser Asp Gln Asp Met Ser Ala Tyr
435 440 445

Leu Ala Glu Gln Ser Arg Leu His Leu Ser Gln Phe Asn Ser Met Ser
450 455 460

Ala Leu His Glu Ile Tyr Ser Tyr Ile Thr Lys Tyr Lys Asp Glu Ile
465 470 475 480

Leu Ala Ala Leu Glu Lys Asp Glu Gln Ala Arg Arg Gln Arg Leu Arg
485 490 495

Ser Lys Leu Glu Gln Val Val Asp Thr Met Ala Leu Ser Ser
500 505 510

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Asp Ser Leu His Lys Ala Pro Lys Lys Lys Ser Ile Lys Ser Ser Ile
1               5                  10                  15

ggc cgt ctc ttt ggc aag aaa gag aag gga cga atg gga ccc cca ggc        96
Gly Arg Leu Phe Gly Lys Lys Glu Lys Gly Arg Met Gly Pro Pro Gly
            20                  25                  30

cgg gac agc tct tct ctg gct gga aca ccc tca gat gag aca ctg gcc       144
Arg Asp Ser Ser Ser Leu Ala Gly Thr Pro Ser Asp Glu Thr Leu Ala
        35                  40                  45

act gac cct ctg ggg cta gcc aag ctg aca ggc cca gga gac aag gac       192
Thr Asp Pro Leu Gly Leu Ala Lys Leu Thr Gly Pro Gly Asp Lys Asp
    50                  55                  60

cga agg aac aag agg aag cat gaa ctc ctg gag gag gcc tgc cgc cag       240
Arg Arg Asn Lys Arg Lys His Glu Leu Leu Glu Glu Ala Cys Arg Gln
65                  70                  75                  80

ggc cta cct ttt gct gcc tgg gac ggg ccc acc gtg gtg tcc tgg ctg       288
Gly Leu Pro Phe Ala Ala Trp Asp Gly Pro Thr Val Val Ser Trp Leu
                85                  90                  95

gag ctg tgg gtg ggc atg cct gcc tgg tat gtg gcc gcc tgc cgg gcc       336
Glu Leu Trp Val Gly Met Pro Ala Trp Tyr Val Ala Ala Cys Arg Ala
            100                 105                 110

aat gtc aag agc ggt gcc atc atg gcc aac ctg tca gac acg aag atc       384
Asn Val Lys Ser Gly Ala Ile Met Ala Asn Leu Ser Asp Thr Lys Ile
        115                 120                 125

cag cgc gag atc ggc atc agc aac ccg ctg cac cga ctc aag cta cgc       432
Gln Arg Glu Ile Gly Ile Ser Asn Pro Leu His Arg Leu Lys Leu Arg
    130                 135                 140

ctc gcc atc cag gag atg gtc tcg ctc acc tcg ccc tca gcc ccc gcc       480
Leu Ala Ile Gln Glu Met Val Ser Leu Thr Ser Pro Ser Ala Pro Ala
145                 150                 155                 160

tcc tcc cgc act tcc aca gga aac gtg tgg atg aca cac gag gag atg       528
Ser Ser Arg Thr Ser Thr Gly Asn Val Trp Met Thr His Glu Glu Met
                165                 170                 175

gag tcc ctt acg gcc acg acc aag ccc gag acc aag gag atc agc tgg       576
Glu Ser Leu Thr Ala Thr Thr Lys Pro Glu Thr Lys Glu Ile Ser Trp
            180                 185                 190

gag cag atc ctg gca tat ggc gac atg aac cac gag tgg gtg ggg aac       624
Glu Gln Ile Leu Ala Tyr Gly Asp Met Asn His Glu Trp Val Gly Asn
        195                 200                 205

gac tgg ctg ccc agc ctg ggg ctg ccc caa tac cgc agc tac ttc atg       672
Asp Trp Leu Pro Ser Leu Gly Leu Pro Gln Tyr Arg Ser Tyr Phe Met
    210                 215                 220

gag tcg ctg gtg gac gct cga atg tta gat cac ctt aac aag aag gag       720
Glu Ser Leu Val Asp Ala Arg Met Leu Asp His Leu Asn Lys Lys Glu
225                 230                 235                 240

ctc cgg ggc caa ctc aag atg gtg gac agc ttt cac agg gtg agt cta       768
Leu Arg Gly Gln Leu Lys Met Val Asp Ser Phe His Arg Val Ser Leu
                245                 250                 255

cat tat gga gtt atg tgc ctg aaa cgg ctc aac tat gac cgg aag gac       816
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His Tyr Gly Val Met Cys Leu Lys Arg Leu Asn Tyr Asp Arg Lys Asp
260 265 270

ctg gag cgg agg cgg gaa gaa agt cag acc cag atc cga gac gtg atg 864
Leu Glu Arg Arg Arg Glu Glu Ser Gln Thr Gln Ile Arg Asp Val Met
275 280 285

gtg tgg tcc aat gag cgg gtc atg ggt tgg gtg tcc ggg ctg ggc ctg 912
Val Trp Ser Asn Glu Arg Val Met Gly Trp Val Ser Gly Leu Gly Leu
290 295 300

aag gaa ttt gcc acg aac ctc acg gag agc ggg gta cac ggg gca ctg 960
Lys Glu Phe Ala Thr Asn Leu Thr Glu Ser Gly Val His Gly Ala Leu
305 310 315 320

ctc gcc ctg gac gag acc ttc gac tac tcc gac ctg gcc ttg ctc ctg 1008
Leu Ala Leu Asp Glu Thr Phe Asp Tyr Ser Asp Leu Ala Leu Leu Leu
325 330 335

cag atc ccc acg cag aat gca cag gcc cgg cag ctt ctg gag aag gaa 1056
Gln Ile Pro Thr Gln Asn Ala Gln Ala Arg Gln Leu Leu Glu Lys Glu
340 345 350

ttc agc aac ctt atc tcc tta ggc aca gac agg cgg ctg gac gag gac 1104
Phe Ser Asn Leu Ile Ser Leu Gly Thr Asp Arg Arg Leu Asp Glu Asp
355 360 365

agc gcc aag tct ttc agc cgc tcc cca tcc tgg cgg aag atg ttc cgg 1152
Ser Ala Lys Ser Phe Ser Arg Ser Pro Ser Trp Arg Lys Met Phe Arg
370 375 380

gag aag gac ctc cga ggc gta act ccc gac tca gct gag atg ttg ccc 1200
Glu Lys Asp Leu Arg Gly Val Thr Pro Asp Ser Ala Glu Met Leu Pro
385 390 395 400

ccc aac ttt cgt tcg gct gca gcg gga gcc ctg ggc tct ccg ggg ctc 1248
Pro Asn Phe Arg Ser Ala Ala Ala Gly Ala Leu Gly Ser Pro Gly Leu
405 410 415

cct ctc cgc aag ctg cag cca gaa ggc cag act tct ggg agt tcc cgg 1296
Pro Leu Arg Lys Leu Gln Pro Glu Gly Gln Thr Ser Gly Ser Ser Arg
420 425 430

gca gac ggc gtt tcg gtc cgg acc tat tcc tgc tag tgcaggcctc 1342
Ala Asp Gly Val Ser Val Arg Thr Tyr Ser Cys
435 440

caggtgacct cactcggacg gaagaatctt cccgaggctg ggctgttccc tctcctgccc 1402

ggactgtggc ctcgccgggg agagcgggcg gggagctc 1440

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Gly Arg Leu Phe Gly Lys Lys Glu Lys Gly Arg Met Gly Pro Pro Gly
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Arg Asp Ser Ser Ser Leu Ala Gly Thr Pro Ser Asp Glu Thr Leu Ala
35 40 45

Thr Asp Pro Leu Gly Leu Ala Lys Leu Thr Gly Pro Gly Asp Lys Asp
50 55 60

Arg Arg Asn Lys Arg Lys His Glu Leu Leu Glu Glu Ala Cys Arg Gln
65 70 75 80

Gly Leu Pro Phe Ala Ala Trp Asp Gly Pro Thr Val Val Ser Trp Leu

85 90 95

Glu Leu Trp Val Gly Met Pro Ala Trp Tyr Val Ala Ala Cys Arg Ala
100 105 110

Asn Val Lys Ser Gly Ala Ile Met Ala Asn Leu Ser Asp Thr Lys Ile
115 120 125

Gln Arg Glu Ile Gly Ile Ser Asn Pro Leu His Arg Leu Lys Leu Arg
130 135 140

Leu Ala Ile Gln Glu Met Val Ser Leu Thr Ser Pro Ser Ala Pro Ala
145 150 155 160

Ser Ser Arg Thr Ser Thr Gly Asn Val Trp Met Thr His Glu Glu Met
165 170 175

Glu Ser Leu Thr Ala Thr Thr Lys Pro Glu Thr Lys Glu Ile Ser Trp
180 185 190

Glu Gln Ile Leu Ala Tyr Gly Asp Met Asn His Glu Trp Val Gly Asn
195 200 205

Asp Trp Leu Pro Ser Leu Gly Leu Pro Gln Tyr Arg Ser Tyr Phe Met
210 215 220

Glu Ser Leu Val Asp Ala Arg Met Leu Asp His Leu Asn Lys Lys Glu
225 230 235 240

Leu Arg Gly Gln Leu Lys Met Val Asp Ser Phe His Arg Val Ser Leu
245 250 255

His Tyr Gly Val Met Cys Leu Lys Arg Leu Asn Tyr Asp Arg Lys Asp
260 265 270

Leu Glu Arg Arg Arg Glu Glu Ser Gln Thr Gln Ile Arg Asp Val Met
275 280 285

Val Trp Ser Asn Glu Arg Val Met Gly Trp Val Ser Gly Leu Gly Leu
290 295 300

Lys Glu Phe Ala Thr Asn Leu Thr Glu Ser Gly Val His Gly Ala Leu
305 310 315 320

Leu Ala Leu Asp Glu Thr Phe Asp Tyr Ser Asp Leu Ala Leu Leu Leu
325 330 335

Gln Ile Pro Thr Gln Asn Ala Gln Ala Arg Gln Leu Leu Glu Lys Glu
340 345 350

Phe Ser Asn Leu Ile Ser Leu Gly Thr Asp Arg Arg Leu Asp Glu Asp
355 360 365

Ser Ala Lys Ser Phe Ser Arg Ser Pro Ser Trp Arg Lys Met Phe Arg
370 375 380

Glu Lys Asp Leu Arg Gly Val Thr Pro Asp Ser Ala Glu Met Leu Pro
385 390 395 400

Pro Asn Phe Arg Ser Ala Ala Ala Gly Ala Leu Gly Ser Pro Gly Leu

405 410 415

Pro Leu Arg Lys Leu Gln Pro Glu Gly Gln Thr Ser Gly Ser Ser Arg
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Ala Asp Gly Val Ser Val Arg Thr Tyr Ser Cys
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Met Glu Gly Ser Gly Gly Gly Ala Gly Glu Arg Ala Pro Leu Leu Gly
1 5 10 15

gcg cgg cgg gcg gcg gcg gcc gcg gcg gcg gct ggg gcg ttc gcg ggc 154
Ala Arg Arg Ala Ala Ala Ala Ala Ala Ala Ala Gly Ala Phe Ala Gly
20 25 30

cgg cgc gcg gcg tgc ggg gcc gtg ctg ctg acg gag ctg ctg gag cgc 202
Arg Arg Ala Ala Cys Gly Ala Val Leu Leu Thr Glu Leu Leu Glu Arg
35 40 45

gcc gct ttc tac ggc atc acg tcc aac ctg gtg cta ttc ctg aac ggg 250
Ala Ala Phe Tyr Gly Ile Thr Ser Asn Leu Val Leu Phe Leu Asn Gly
50 55 60

gcg ccg ttc tgc tgg gag ggc gcg cag gcc agc gag gcg ctg ctg ctc 298
Ala Pro Phe Cys Trp Glu Gly Ala Gln Ala Ser Glu Ala Leu Leu Leu
65 70 75 80

ttc atg ggc ctc acc tac ctg ggc tcg ccg ttc gga ggc tgg ctg gcc 346
Phe Met Gly Leu Thr Tyr Leu Gly Ser Pro Phe Gly Gly Trp Leu Ala
85 90 95

gac gcg cgg ctg ggc cgg gcg cgc gcc atc ctg ctg agc ctg gcg ctc 394
Asp Ala Arg Leu Gly Arg Ala Arg Ala Ile Leu Leu Ser Leu Ala Leu
100 105 110

tac ctg ctg ggc atg ctg gcc ttc ccg ctg ctg gcc gcg ccc gcc acg 442
Tyr Leu Leu Gly Met Leu Ala Phe Pro Leu Leu Ala Ala Pro Ala Thr
115 120 125

cga gcc gcg ctc tgc ggt tcc gcg cgc ctg ctc aac tgc acg gcg cct 490
Arg Ala Ala Leu Cys Gly Ser Ala Arg Leu Leu Asn Cys Thr Ala Pro
130 135 140

ggt ccc gac gcc gcc gcc cgc tgc tgc tca ccg gcc acc ttc gcg ggg 538
Gly Pro Asp Ala Ala Ala Arg Cys Cys Ser Pro Ala Thr Phe Ala Gly
145 150 155 160

ctg gtg ctg gtg ggc ctg ggc gtg gcc acc gtc aag gcc aac atc acg 586
Leu Val Leu Val Gly Leu Gly Val Ala Thr Val Lys Ala Asn Ile Thr
165 170 175

ccc ttc ggc gcc gac cag gtt aaa gat cga ggt ccg gaa gcc act agg 634
Pro Phe Gly Ala Asp Gln Val Lys Asp Arg Gly Pro Glu Ala Thr Arg
180 185 190

aga ttt ttt aat tgg ttt tat tgg agc att aac ctg gga gcg atc ctg 682
Arg Phe Phe Asn Trp Phe Tyr Trp Ser Ile Asn Leu Gly Ala Ile Leu
195 200 205

tcg tta ggt ggc att gcc tat att cag cag aac gtc agc ttt gtc act 730
Ser Leu Gly Gly Ile Ala Tyr Ile Gln Gln Asn Val Ser Phe Val Thr
210 215 220

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ggt tat gcg atc ccc act gtc tgc gtc ggc ctt gct ttt gtg gtc ttc      778
Gly Tyr Ala Ile Pro Thr Val Cys Val Gly Leu Ala Phe Val Val Phe
225                 230                 235                 240

ctc tgt ggc cag agc gtt ttc atc acc aag cct cct gat ggc agt gcc      826
Leu Cys Gly Gln Ser Val Phe Ile Thr Lys Pro Pro Asp Gly Ser Ala
                245                 250                 255

ttc acc gac atg ttc aag ata ctg acg tat tcc tgc tgt tcc cag aag      874
Phe Thr Asp Met Phe Lys Ile Leu Thr Tyr Ser Cys Cys Ser Gln Lys
            260                 265                 270

cga agt gga gag cgc cag agt aat ggt gaa ggc att gga gtc ttt cag      922
Arg Ser Gly Glu Arg Gln Ser Asn Gly Glu Gly Ile Gly Val Phe Gln
        275                 280                 285

caa tct tct aaa caa agt ctg ttt gat tca tgt aag atg tct cat ggt      970
Gln Ser Ser Lys Gln Ser Leu Phe Asp Ser Cys Lys Met Ser His Gly
    290                 295                 300

ggg cca ttt aca gaa gag aaa gtg gaa gat gtg aaa gct ctg gtc aag     1018
Gly Pro Phe Thr Glu Glu Lys Val Glu Asp Val Lys Ala Leu Val Lys
305                 310                 315                 320

att gtc cct gtt ttc ttg gct ttg ata cct tac tgg aca gtg tat ttc     1066
Ile Val Pro Val Phe Leu Ala Leu Ile Pro Tyr Trp Thr Val Tyr Phe
                325                 330                 335

caa atg cag aca aca tat gtt tta cag agt ctt cat ttg agg att cca     1114
Gln Met Gln Thr Thr Tyr Val Leu Gln Ser Leu His Leu Arg Ile Pro
            340                 345                 350

gaa att tca aat att aca acc act cct cac acg ctc cct gca gcc tgg     1162
Glu Ile Ser Asn Ile Thr Thr Thr Pro His Thr Leu Pro Ala Ala Trp
        355                 360                 365

ctg acc atg ttt gat gct gtg ctc atc ctc ctg ctc atc cct ctg aag     1210
Leu Thr Met Phe Asp Ala Val Leu Ile Leu Leu Leu Ile Pro Leu Lys
    370                 375                 380

gac aaa ctg gtc gat ccc att ttg aga aga cat ggc ctg ctc cca tcc     1258
Asp Lys Leu Val Asp Pro Ile Leu Arg Arg His Gly Leu Leu Pro Ser
385                 390                 395                 400

tcc ctg aag agg atc gcc gtg ggc atg ttc ttt gtc atg tgc tcg gcc     1306
Ser Leu Lys Arg Ile Ala Val Gly Met Phe Phe Val Met Cys Ser Ala
                405                 410                 415

ttt gct gca gga att ttg gag agt aaa agg ctg aac ctt gtt aaa gag     1354
Phe Ala Ala Gly Ile Leu Glu Ser Lys Arg Leu Asn Leu Val Lys Glu
            420                 425                 430

aaa acc att aat cag acc atc ggc aac gtc gtc tac cat gct gcc gat     1402
Lys Thr Ile Asn Gln Thr Ile Gly Asn Val Val Tyr His Ala Ala Asp
        435                 440                 445

ctg tcg ctg tgg tgg cag gtg ccg cag tac ttg ctg att ggg atc agc     1450
Leu Ser Leu Trp Trp Gln Val Pro Gln Tyr Leu Leu Ile Gly Ile Ser
    450                 455                 460

gag atc ttt gca agt atc gca ggc ctg gaa ttt gca tac tca gct gcc     1498
Glu Ile Phe Ala Ser Ile Ala Gly Leu Glu Phe Ala Tyr Ser Ala Ala
465                 470                 475                 480

ccc aag tcc atg cag agt gcc ata atg ggc ttg ttc ttt ttc ttc tct     1546
Pro Lys Ser Met Gln Ser Ala Ile Met Gly Leu Phe Phe Phe Phe Ser
                485                 490                 495

ggc gtc ggg tcg ttc gtg ggt tct gga ctg ctg gca ctg gtg tct atc     1594
Gly Val Gly Ser Phe Val Gly Ser Gly Leu Leu Ala Leu Val Ser Ile
            500                 505                 510

aaa gcc atc gga tgg atg agc agt cac aca gac ttt ggt aat att aac     1642
Lys Ala Ile Gly Trp Met Ser Ser His Thr Asp Phe Gly Asn Ile Asn
        515                 520                 525

ggc tgc tat ttg aac tat tac ttt ttt ctt ctg gct gct att caa gga     1690
Gly Cys Tyr Leu Asn Tyr Tyr Phe Phe Leu Leu Ala Ala Ile Gln Gly
    530                 535                 540
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gct acc ctc ctg ctt ttc ctc att att tct gtg aaa tat gac cat cat 1738
Ala Thr Leu Leu Leu Phe Leu Ile Ile Ser Val Lys Tyr Asp His His
545 550 555 560

cga gac cat cag cga tca aga gcc aat ggc gtg ccc acc agc agg agg 1786
Arg Asp His Gln Arg Ser Arg Ala Asn Gly Val Pro Thr Ser Arg Arg
565 570 575

gcc tga ccttcctgag gccatgtgcg gtttctgagg ctgacatgtc agtaactgac 1842
Ala

tggggtgcac tgagaacagg caagacttta aattcccata aaatgtctga cttcactgaa 1902

acttgcatgt tgcctggatt gatttcttct ttccctctat ccaaaggagc ttggtaagtg 1962

ccttactgca gcgtgtctcc tggcacgctg ggccctccgg gaggagagct gcagatttcg 2022

agtatgtcgc ttgtcattca aggtctctgt gaatcctcta gctgggttcc ctttttttaca 2082

gaaactcaca aatggagatt gcaaagtctt ggggaactcc acgtgttagt tggcatccca 2142

gtttcttaaa caaatagtat cacctgcttc ccatagccat atctcactgt aaaaaaaaaa 2202

aattaataaa ctgttactta tatttaagaa agtgaggatt ttttttttt aaagataaaa 2262

gcatggtcag atgctgcaag gattttacat aaatgccata tttatggttt ccttcctgag 2322

aacagtcttg ctcttgccat gttctttgat ttaggctggt agtaaacaca tttcatctgc 2382

tgcttcaaaa agtacttact ttttaaacca tcaacattac ttttctttct taaggcaagg 2442

catgcataag agtcatttga gaccatgtgt cccatctcaa gccacagagc aactcacagg 2502

gtacttcaca ccttacctag tcagagtgct tatatatagc tttattttgg tacgattgag 2562

actaaagact gatcatggtt gtatgtaagg aaaacattct tttgaacaga aatagtgtaa 2622

ttaaaaataa ttgaaagtgt taaatgtgaa cttgagctgt ttgaccagcc acatttttgt 2682

attgttactg tacgtgtatc tggggcttct ccgtttgtta atacttttttc tgtatttgtt 2742

gctgtatttt tggcataact ttattataaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2802

aaaaa 2807

<210> 64
<211> 577
<212> PRT
<213> Homo sapiens

<400> 64

Met Glu Gly Ser Gly Gly Gly Ala Gly Glu Arg Ala Pro Leu Leu Gly
1 5 10 15

Ala Arg Arg Ala Ala Ala Ala Ala Ala Ala Ala Gly Ala Phe Ala Gly
20 25 30

Arg Arg Ala Ala Cys Gly Ala Val Leu Leu Thr Glu Leu Leu Glu Arg
35 40 45

Ala Ala Phe Tyr Gly Ile Thr Ser Asn Leu Val Leu Phe Leu Asn Gly
50 55 60

Ala Pro Phe Cys Trp Glu Gly Ala Gln Ala Ser Glu Ala Leu Leu Leu
65 70 75 80

Phe Met Gly Leu Thr Tyr Leu Gly Ser Pro Phe Gly Gly Trp Leu Ala
85 90 95

Asp Ala Arg Leu Gly Arg Ala Arg Ala Ile Leu Leu Ser Leu Ala Leu
100 105 110

Tyr Leu Leu Gly Met Leu Ala Phe Pro Leu Leu Ala Ala Pro Ala Thr
115 120 125

Arg Ala Ala Leu Cys Gly Ser Ala Arg Leu Leu Asn Cys Thr Ala Pro
130 135 140

Gly Pro Asp Ala Ala Ala Arg Cys Cys Ser Pro Ala Thr Phe Ala Gly
145 150 155 160

Leu Val Leu Val Gly Leu Gly Val Ala Thr Val Lys Ala Asn Ile Thr
165 170 175

Pro Phe Gly Ala Asp Gln Val Lys Asp Arg Gly Pro Glu Ala Thr Arg
180 185 190

Arg Phe Phe Asn Trp Phe Tyr Trp Ser Ile Asn Leu Gly Ala Ile Leu
195 200 205

Ser Leu Gly Gly Ile Ala Tyr Ile Gln Gln Asn Val Ser Phe Val Thr
210 215 220

Gly Tyr Ala Ile Pro Thr Val Cys Val Gly Leu Ala Phe Val Val Phe
225 230 235 240

Leu Cys Gly Gln Ser Val Phe Ile Thr Lys Pro Pro Asp Gly Ser Ala
245 250 255

Phe Thr Asp Met Phe Lys Ile Leu Thr Tyr Ser Cys Cys Ser Gln Lys
260 265 270

Arg Ser Gly Glu Arg Gln Ser Asn Gly Glu Gly Ile Gly Val Phe Gln
275 280 285

Gln Ser Ser Lys Gln Ser Leu Phe Asp Ser Cys Lys Met Ser His Gly
290 295 300

Gly Pro Phe Thr Glu Glu Lys Val Glu Asp Val Lys Ala Leu Val Lys
305 310 315 320

Ile Val Pro Val Phe Leu Ala Leu Ile Pro Tyr Trp Thr Val Tyr Phe
325 330 335

Gln Met Gln Thr Thr Tyr Val Leu Gln Ser Leu His Leu Arg Ile Pro
340 345 350

Glu Ile Ser Asn Ile Thr Thr Thr Pro His Thr Leu Pro Ala Ala Trp
355 360 365

Leu Thr Met Phe Asp Ala Val Leu Ile Leu Leu Leu Ile Pro Leu Lys
370 375 380

Asp Lys Leu Val Asp Pro Ile Leu Arg Arg His Gly Leu Leu Pro Ser
385 390 395 400

Ser Leu Lys Arg Ile Ala Val Gly Met Phe Phe Val Met Cys Ser Ala
405 410 415

Phe Ala Ala Gly Ile Leu Glu Ser Lys Arg Leu Asn Leu Val Lys Glu
420 425 430

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Lys Thr Ile Asn Gln Thr Ile Gly Asn Val Val Tyr His Ala Ala Asp
        435                 440                 445

Leu Ser Leu Trp Trp Gln Val Pro Gln Tyr Leu Leu Ile Gly Ile Ser
    450                 455                 460

Glu Ile Phe Ala Ser Ile Ala Gly Leu Glu Phe Ala Tyr Ser Ala Ala
465                 470                 475                 480

Pro Lys Ser Met Gln Ser Ala Ile Met Gly Leu Phe Phe Phe Phe Ser
                485                 490                 495

Gly Val Gly Ser Phe Val Gly Ser Gly Leu Leu Ala Leu Val Ser Ile
            500                 505                 510

Lys Ala Ile Gly Trp Met Ser Ser His Thr Asp Phe Gly Asn Ile Asn
        515                 520                 525

Gly Cys Tyr Leu Asn Tyr Tyr Phe Phe Leu Leu Ala Ala Ile Gln Gly
    530                 535                 540

Ala Thr Leu Leu Leu Phe Leu Ile Ile Ser Val Lys Tyr Asp His His
545                 550                 555                 560

Arg Asp His Gln Arg Ser Arg Ala Asn Gly Val Pro Thr Ser Arg Arg
                565                 570                 575

Ala
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<210> 65
<211> 1982
<212> DNA
<213> Homo sapiens

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<222> (63)..(1460)
<223>

<400> 65

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cc atg gga ggg gcc gtg gtg gac gag ggc ccc aca ggc gtc aag gcc        107
   Met Gly Gly Ala Val Val Asp Glu Gly Pro Thr Gly Val Lys Ala
   1               5                  10                  15

cct gac ggc ggc tgg ggc tgg gcc gtg ctc ttc ggc tgt ttc gtc atc      155
Pro Asp Gly Gly Trp Gly Trp Ala Val Leu Phe Gly Cys Phe Val Ile
               20                  25                  30

act ggc ttc tcc tac gcc ttc ccc aag gcc gtc agt gtc ttc ttc aag      203
Thr Gly Phe Ser Tyr Ala Phe Pro Lys Ala Val Ser Val Phe Phe Lys
           35                  40                  45

gag ctc ata cag gag ttt ggg atc ggc tac agc gac aca gcc tgg atc      251
Glu Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile
       50                  55                  60

tcc tcc atc ctg ctg gcc atg ctc tac ggg aca ggt ccg ctc tgc agt      299
Ser Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser
   65                  70                  75

gtg tgc gtg aac cgc ttt ggc tgc cgg ccc gtc atg ctt gtg ggg ggt      347
Val Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly
80                  85                  90                  95

ctc ttt gcg tcg ctg ggc atg gtg gct gcg tcc ttt tgc cgg agc atc      395
Leu Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile
               100                 105                 110
```

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atc cag gtc tac ctc acc act ggg gtc atc acg ggg ttg ggt ttg gca      443
Ile Gln Val Tyr Leu Thr Thr Gly Val Ile Thr Gly Leu Gly Leu Ala
            115                 120                 125

ctc aac ttc cag ccc tcg ctc atc atg ctg aac cgc tac ttc agc aag      491
Leu Asn Phe Gln Pro Ser Leu Ile Met Leu Asn Arg Tyr Phe Ser Lys
        130                 135                 140

cgg cgc ccc atg gcc aac ggg ctg gcg gca gca ggt agc cct gtc ttc      539
Arg Arg Pro Met Ala Asn Gly Leu Ala Ala Ala Gly Ser Pro Val Phe
    145                 150                 155

ctg tgt gcc ctg agc ccg ctg ggg cag ctg ctg cag gac cgc tac ggc      587
Leu Cys Ala Leu Ser Pro Leu Gly Gln Leu Leu Gln Asp Arg Tyr Gly
160                 165                 170                 175

tgg cgg ggc ggc ttc ctc atc ctg ggc ggc ctg ctg ctc aac tgc tgc      635
Trp Arg Gly Gly Phe Leu Ile Leu Gly Gly Leu Leu Leu Asn Cys Cys
                180                 185                 190

gtg tgt gcc gca ctc atg agg ccc ctg gtg gtc acg gcc cag ccg ggc      683
Val Cys Ala Ala Leu Met Arg Pro Leu Val Val Thr Ala Gln Pro Gly
            195                 200                 205

tcg ggg ccg ccg cga ccc tcc cgg cgc ctg cta gac ctg agc gtc ttc      731
Ser Gly Pro Pro Arg Pro Ser Arg Arg Leu Leu Asp Leu Ser Val Phe
        210                 215                 220

cgg gac cgc ggc ttt gtg ctt tac gcc gtg gcc gcc tcg gtc atg gtg      779
Arg Asp Arg Gly Phe Val Leu Tyr Ala Val Ala Ala Ser Val Met Val
    225                 230                 235

ctg ggg ctc ttc gtc ccg ccc gtg ttc gtg gtg agc tac gcc aag gac      827
Leu Gly Leu Phe Val Pro Pro Val Phe Val Val Ser Tyr Ala Lys Asp
240                 245                 250                 255

ctg ggc gtg ccc gac acc aag gcc gcc ttc ctg ctc acc atc ctg ggc      875
Leu Gly Val Pro Asp Thr Lys Ala Ala Phe Leu Leu Thr Ile Leu Gly
                260                 265                 270

ttc att gac atc ttc gcg cgg ccg gcc gcg ggc ttc gtg gcg ggg ctt      923
Phe Ile Asp Ile Phe Ala Arg Pro Ala Ala Gly Phe Val Ala Gly Leu
            275                 280                 285

ggg aag gtg cgg ccc tac tcc gtc tac ctc ttc agc ttc tcc atg ttc      971
Gly Lys Val Arg Pro Tyr Ser Val Tyr Leu Phe Ser Phe Ser Met Phe
        290                 295                 300

ttc aac ggc ctc gcg gac ctg gcg ggc tct acg gcg ggc gac tac ggc     1019
Phe Asn Gly Leu Ala Asp Leu Ala Gly Ser Thr Ala Gly Asp Tyr Gly
    305                 310                 315

ggc ctc gtg gtc ttc tgc atc ttc ttt ggc atc tcc tac ggc atg gtg     1067
Gly Leu Val Val Phe Cys Ile Phe Phe Gly Ile Ser Tyr Gly Met Val
320                 325                 330                 335

ggg gcc ctg cag ttc gag gtg ctc atg gcc atc gtg ggc acc cac aag     1115
Gly Ala Leu Gln Phe Glu Val Leu Met Ala Ile Val Gly Thr His Lys
                340                 345                 350

ttc tcc agt gcc att ggc ctg gtg ctg ctg atg gag gcg gtg gcc gtg     1163
Phe Ser Ser Ala Ile Gly Leu Val Leu Leu Met Glu Ala Val Ala Val
            355                 360                 365

ctc gtc ggg ccc cct tcg gga ggc aaa ctc ctg gat gcg acc cac gtc     1211
Leu Val Gly Pro Pro Ser Gly Gly Lys Leu Leu Asp Ala Thr His Val
        370                 375                 380

tac atg tac gtg ttc atc ctg gcg ggg gcc gag gtg ctc acc tcc tcc     1259
Tyr Met Tyr Val Phe Ile Leu Ala Gly Ala Glu Val Leu Thr Ser Ser
    385                 390                 395

ctg att ttg ctg ctg ctg ggc aac ttc ttc tgc att agg aag aag ccc aaa 1307
Leu Ile Leu Leu Leu Leu Gly Asn Phe Phe Cys Ile Arg Lys Lys Pro Lys
400                 405                 410                 415

gag cca cag cct gag gtg gcg gcc gcg gag gag gag aag ctc cac aag     1355
Glu Pro Gln Pro Glu Val Ala Ala Ala Glu Glu Glu Lys Leu His Lys
                420                 425                 430
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cct cct gca gac tcg ggg gtg gac ttg cgg gag gtg gag cat ttc ctg 1403
Pro Pro Ala Asp Ser Gly Val Asp Leu Arg Glu Val Glu His Phe Leu
435 440 445

aag gct gag cct gag aaa aac ggg gag gtg gtt cac acc ccg gaa aca 1451
Lys Ala Glu Pro Glu Lys Asn Gly Glu Val Val His Thr Pro Glu Thr
450 455 460

agt gtc tga gtggctgggc ggggccggca ggcacaggga ggaggtacag 1500
Ser Val
465

aagccggcaa cgcttgctat ttattttaca aactggactg gctcaggcag ggccacggct 1560

gggctccagc tgccggccca gcggatcgtc gcccgatcag tgttttgagg gggaaggtgg 1620

cggggtggga accgtgtcat tccagagtgg atctgcggtg aagccaagcc gcaaggttac 1680

aaggcatcct caccaggggc cccgcctgct gctcccaggt ggcctgcggc cactgctatg 1740

ctcaaggacc tggaaaccca tgcttcgaga caacgtgact ttaatgggag ggtgggtggg 1800

ccgcagacag gctggcaggg caggtgctgc gtggggccct ctccagcccg tcctaccctg 1860

ggctcacatg gggcctgtgc ccacccctct tgagtgtctt ggggacagct ctttccaccc 1920

ctggaagatg gaaataaacc tgcgtgtggg tggagtgttc tcgtgccgaa ttcaaaaagc 1980

tt 1982

<210> 66
<211> 465
<212> PRT
<213> Homo sapiens

<400> 66

Met Gly Gly Ala Val Val Asp Glu Gly Pro Thr Gly Val Lys Ala Pro
1 5 10 15

Asp Gly Gly Trp Gly Trp Ala Val Leu Phe Gly Cys Phe Val Ile Thr
20 25 30

Gly Phe Ser Tyr Ala Phe Pro Lys Ala Val Ser Val Phe Phe Lys Glu
35 40 45

Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile Ser
50 55 60

Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser Val
65 70 75 80

Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly Leu
85 90 95

Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile Ile
100 105 110

Gln Val Tyr Leu Thr Thr Gly Val Ile Thr Gly Leu Gly Leu Ala Leu
115 120 125

Asn Phe Gln Pro Ser Leu Ile Met Leu Asn Arg Tyr Phe Ser Lys Arg
130 135 140

Arg Pro Met Ala Asn Gly Leu Ala Ala Ala Gly Ser Pro Val Phe Leu
145 150 155 160

Cys Ala Leu Ser Pro Leu Gly Gln Leu Leu Gln Asp Arg Tyr Gly Trp
165 170 175

Arg Gly Gly Phe Leu Ile Leu Gly Gly Leu Leu Leu Asn Cys Cys Val
180 185 190

Cys Ala Ala Leu Met Arg Pro Leu Val Val Thr Ala Gln Pro Gly Ser
195 200 205

Gly Pro Pro Arg Pro Ser Arg Arg Leu Leu Asp Leu Ser Val Phe Arg
210 215 220

Asp Arg Gly Phe Val Leu Tyr Ala Val Ala Ala Ser Val Met Val Leu
225 230 235 240

Gly Leu Phe Val Pro Pro Val Phe Val Val Ser Tyr Ala Lys Asp Leu
245 250 255

Gly Val Pro Asp Thr Lys Ala Ala Phe Leu Leu Thr Ile Leu Gly Phe
260 265 270

Ile Asp Ile Phe Ala Arg Pro Ala Ala Gly Phe Val Ala Gly Leu Gly
275 280 285

Lys Val Arg Pro Tyr Ser Val Tyr Leu Phe Ser Phe Ser Met Phe Phe
290 295 300

Asn Gly Leu Ala Asp Leu Ala Gly Ser Thr Ala Gly Asp Tyr Gly Gly
305 310 315 320

Leu Val Val Phe Cys Ile Phe Phe Gly Ile Ser Tyr Gly Met Val Gly
325 330 335

Ala Leu Gln Phe Glu Val Leu Met Ala Ile Val Gly Thr His Lys Phe
340 345 350

Ser Ser Ala Ile Gly Leu Val Leu Leu Met Glu Ala Val Ala Val Leu
355 360 365

Val Gly Pro Pro Ser Gly Gly Lys Leu Leu Asp Ala Thr His Val Tyr
370 375 380

Met Tyr Val Phe Ile Leu Ala Gly Ala Glu Val Leu Thr Ser Ser Leu
385 390 395 400

Ile Leu Leu Leu Gly Asn Phe Phe Cys Ile Arg Lys Lys Pro Lys Glu
405 410 415

Pro Gln Pro Glu Val Ala Ala Ala Glu Glu Glu Lys Leu His Lys Pro
420 425 430

Pro Ala Asp Ser Gly Val Asp Leu Arg Glu Val Glu His Phe Leu Lys
435 440 445

Ala Glu Pro Glu Lys Asn Gly Glu Val Val His Thr Pro Glu Thr Ser
450 455 460

Val
465

<210> 67
<211> 2856
<212> DNA

<213> Homo sapiens

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<222> (591)..(2216)
<223>

<400> 67
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cctcccggac ctaagagcct gggtcccctg tttccggagg tccgcttccc ggcccccaga 120

ttctggcatc ccagccctca gtgtccaaga cccaggcagc ccgggtcccc gcctcccgga 180

tccaggcgtc cgggatctgc gccaccagaa cctagcctcc tgcagacctc cgccatctgg 240

gggcactcaa cctcctggag ccaagggccc cacgtcccac ccagagaaac tctcgtattc 300

ccagctccta gggccaagga acccgggcgc tccgaactcc cagctttcgg acatctggca 360

cacggggcag agcagagaag ctcagcgccc agcctgggga atttaaacac tccagcttcc 420

aagagccaag gaacttcagt gctgtgaact cacaactcta aggagccctc caaagttcca 480

gtctccaggt gctgttactc aactcagtcc taggaacgtc gggtcctggg aaggagccca 540

agcgctccca gccagcttcc aggcgctaag aaaccccggt gcttcccatc atg gtg 596
Met Val
1

gcc gat cct cct cga gac tcc aag ggg ctc gca gcg gcg gag ccc acc 644
Ala Asp Pro Pro Arg Asp Ser Lys Gly Leu Ala Ala Ala Glu Pro Thr
5 10 15

gcc aac ggg ggc ctg gcg ctg gcc tcc atc gag gac caa ggc gcg gca 692
Ala Asn Gly Gly Leu Ala Leu Ala Ser Ile Glu Asp Gln Gly Ala Ala
20 25 30

gca ggc ggc tac tgc ggt tcc cgg gac cag gtg cgc cgc tgc ctt cga 740
Ala Gly Gly Tyr Cys Gly Ser Arg Asp Gln Val Arg Arg Cys Leu Arg
35 40 45 50

gcc aac ctg ctt gtg ctg ctg aca gtg gtg gcc gtg gtg gcc ggc gtg 788
Ala Asn Leu Leu Val Leu Leu Thr Val Val Ala Val Val Ala Gly Val
55 60 65

gcg ctg gga ctg ggg gtg tcg ggg gcc ggg ggt gcg ctg gcg ttg ggc 836
Ala Leu Gly Leu Gly Val Ser Gly Ala Gly Gly Ala Leu Ala Leu Gly
70 75 80

ccg gag cgc ttg agc gcc ttc gtc ttc ccg ggc gag ctg ctg ctg cgt 884
Pro Glu Arg Leu Ser Ala Phe Val Phe Pro Gly Glu Leu Leu Leu Arg
85 90 95

ctg ctg cgg atg atc atc ttg ccg ctg gtg gtg tgc agc ttg atc ggc 932
Leu Leu Arg Met Ile Ile Leu Pro Leu Val Val Cys Ser Leu Ile Gly
100 105 110

ggc gcc gcc agc ctg gac ccc ggc gcg ctc ggc cgt ctg ggc gcc tgg 980
Gly Ala Ala Ser Leu Asp Pro Gly Ala Leu Gly Arg Leu Gly Ala Trp
115 120 125 130

gcg ctg ctc ttt ttc ctg gtc acc acg ctg ctg gcg tcg gcg ctc gga 1028
Ala Leu Leu Phe Phe Leu Val Thr Thr Leu Leu Ala Ser Ala Leu Gly
135 140 145

gtg ggc ttg gcg ctg gct ctg cag ccg ggc gcc gcc tcc gcc gcc atc 1076
Val Gly Leu Ala Leu Ala Leu Gln Pro Gly Ala Ala Ser Ala Ala Ile
150 155 160

aac gcc tcc gtg gga gcc gcg ggc agt gcc gaa aat gcc ccc agc aag 1124
Asn Ala Ser Val Gly Ala Ala Gly Ser Ala Glu Asn Ala Pro Ser Lys
165 170 175

gag gtg ctc gat tcg ttc ctg gat ctt gcg aga aat atc ttc cct tcc 1172
Glu Val Leu Asp Ser Phe Leu Asp Leu Ala Arg Asn Ile Phe Pro Ser
180 185 190

aac ctg gtg tca gca gcc ttt cgc tca tac tct acc acc tat gaa gag 1220
Asn Leu Val Ser Ala Ala Phe Arg Ser Tyr Ser Thr Thr Tyr Glu Glu

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195                 200                 205                 210

agg aat atc acc gga acc agg gtg aag gtg ccc gtg ggg cag gag gtg      1268
Arg Asn Ile Thr Gly Thr Arg Val Lys Val Pro Val Gly Gln Glu Val
                215                 220                 225

gag ggg atg aac atc ctg ggc ttg gta gtg ttt gcc atc gtc ttt ggt      1316
Glu Gly Met Asn Ile Leu Gly Leu Val Val Phe Ala Ile Val Phe Gly
            230                 235                 240

gtg gcg ctg cgg aag ctg ggg cct gaa ggg gag ctg ctt atc cgc ttc      1364
Val Ala Leu Arg Lys Leu Gly Pro Glu Gly Glu Leu Leu Ile Arg Phe
        245                 250                 255

ttc aac tcc ttc aat gag gcc acc atg gtt ctg gtc tcc tgg atc atg      1412
Phe Asn Ser Phe Asn Glu Ala Thr Met Val Leu Val Ser Trp Ile Met
    260                 265                 270

tgg tac gcc cct gtg ggc atc atg ttc ctg gtg gct ggc aag atc gtg      1460
Trp Tyr Ala Pro Val Gly Ile Met Phe Leu Val Ala Gly Lys Ile Val
275                 280                 285                 290

gag atg gag gat gtg ggt tta ctc ttt gcc cgc ctt ggc aag tac att      1508
Glu Met Glu Asp Val Gly Leu Leu Phe Ala Arg Leu Gly Lys Tyr Ile
                295                 300                 305

ctg tgc tgc ctg ctg ggt cac gcc atc cat ggg ctc ctg gta ctg ccc      1556
Leu Cys Cys Leu Leu Gly His Ala Ile His Gly Leu Leu Val Leu Pro
            310                 315                 320

ctc atc tac ttc ctc ttc acc cgc aaa aac ccc tac cgc ttc ctg tgg      1604
Leu Ile Tyr Phe Leu Phe Thr Arg Lys Asn Pro Tyr Arg Phe Leu Trp
        325                 330                 335

ggc atc gtg acg ccg ctg gcc act gcc ttt ggg acc tct tcc agt tcc      1652
Gly Ile Val Thr Pro Leu Ala Thr Ala Phe Gly Thr Ser Ser Ser Ser
    340                 345                 350

gcc acg ctg ccg ctg atg atg aag tgc gtg gag gag aat aat ggc gtg      1700
Ala Thr Leu Pro Leu Met Met Lys Cys Val Glu Glu Asn Asn Gly Val
355                 360                 365                 370

gcc aag cac atc agc cgt ttc atc ctg ccc atc ggc gcc acc gtc aac      1748
Ala Lys His Ile Ser Arg Phe Ile Leu Pro Ile Gly Ala Thr Val Asn
                375                 380                 385

atg gac ggt gcc gcg ctc ttc cag tgc gtg gcc gca gtg ttc att gca      1796
Met Asp Gly Ala Ala Leu Phe Gln Cys Val Ala Ala Val Phe Ile Ala
            390                 395                 400

cag ctc agc cag cag tcc ttg gac ttc gta aag atc atc acc atc ctg      1844
Gln Leu Ser Gln Gln Ser Leu Asp Phe Val Lys Ile Ile Thr Ile Leu
        405                 410                 415

gtc acg gcc aca gcg tcc agc gtg ggg gca gcg ggc atc cct gct gga      1892
Val Thr Ala Thr Ala Ser Ser Val Gly Ala Ala Gly Ile Pro Ala Gly
    420                 425                 430

ggt gtc ctc act ctg gcc atc atc ctc gaa gca gtc aac ctc ccg gtc      1940
Gly Val Leu Thr Leu Ala Ile Ile Leu Glu Ala Val Asn Leu Pro Val
435                 440                 445                 450

gac cat atc tcc ttg atc ctg gct gtg gac tgg cta gtc gac cgg tcc      1988
Asp His Ile Ser Leu Ile Leu Ala Val Asp Trp Leu Val Asp Arg Ser
                455                 460                 465

tgt acc gtc ctc aat gta gaa ggt gac gct ctg ggg gca gga ctc ctc      2036
Cys Thr Val Leu Asn Val Glu Gly Asp Ala Leu Gly Ala Gly Leu Leu
            470                 475                 480

caa aat tat gtg gac cgt acg gag tcg aga agc aca gag cct gag ttg      2084
Gln Asn Tyr Val Asp Arg Thr Glu Ser Arg Ser Thr Glu Pro Glu Leu
        485                 490                 495

ata caa gtg aag agt gag ctg ccc ctg gat ccg ctg cca gtc ccc act      2132
Ile Gln Val Lys Ser Glu Leu Pro Leu Asp Pro Leu Pro Val Pro Thr
    500                 505                 510

gag gaa gga aac ccc ctc ctc aaa cac tat cgg ggg ccc gca ggg gat      2180
Glu Glu Gly Asn Pro Leu Leu Lys His Tyr Arg Gly Pro Ala Gly Asp
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515 520 525 530

gcc acg gtc gcc tct gag aag gaa tca gtc atg taa accccgggag 2226
Ala Thr Val Ala Ser Glu Lys Glu Ser Val Met
535 540

ggaccttccc tgccctgctg ggggtgctct ttggacactg gattatgagg aatggataaa 2286
tggatgagct agggctctgg gggtctgcct gcacactctg gggagccagg ggccccagca 2346
ccctccagga caggagatct gggatgcctg gctgctggag tacatgtgtt cacaagggtt 2406
actcctcaaa acccccagtt ctcactcatg tccccaactc aaggctagaa aacagcaaga 2466
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tgtgtgtgtg tgtgtgtgtg tgtgttctgt gacctcctgt ccccatggta cgtcccaccc 2706
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gtgtcaacta tttaaaaaaa aaaaaaaaaa 2856

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<211> 541
<212> PRT
<213> Homo sapiens

<400> 68

Met Val Ala Asp Pro Pro Arg Asp Ser Lys Gly Leu Ala Ala Ala Glu
1 5 10 15

Pro Thr Ala Asn Gly Gly Leu Ala Leu Ala Ser Ile Glu Asp Gln Gly
20 25 30

Ala Ala Ala Gly Gly Tyr Cys Gly Ser Arg Asp Gln Val Arg Arg Cys
35 40 45

Leu Arg Ala Asn Leu Leu Val Leu Leu Thr Val Val Ala Val Val Ala
50 55 60

Gly Val Ala Leu Gly Leu Gly Val Ser Gly Ala Gly Gly Ala Leu Ala
65 70 75 80

Leu Gly Pro Glu Arg Leu Ser Ala Phe Val Phe Pro Gly Glu Leu Leu
85 90 95

Leu Arg Leu Leu Arg Met Ile Ile Leu Pro Leu Val Val Cys Ser Leu
100 105 110

Ile Gly Gly Ala Ala Ser Leu Asp Pro Gly Ala Leu Gly Arg Leu Gly
115 120 125

Ala Trp Ala Leu Leu Phe Phe Leu Val Thr Thr Leu Leu Ala Ser Ala
130 135 140

Leu Gly Val Gly Leu Ala Leu Ala Leu Gln Pro Gly Ala Ala Ser Ala
145 150 155 160

Ala Ile Asn Ala Ser Val Gly Ala Ala Gly Ser Ala Glu Asn Ala Pro
165 170 175

Ser Lys Glu Val Leu Asp Ser Phe Leu Asp Leu Ala Arg Asn Ile Phe
180 185 190

Pro Ser Asn Leu Val Ser Ala Ala Phe Arg Ser Tyr Ser Thr Thr Tyr
195 200 205

Glu Glu Arg Asn Ile Thr Gly Thr Arg Val Lys Val Pro Val Gly Gln
210 215 220

Glu Val Glu Gly Met Asn Ile Leu Gly Leu Val Val Phe Ala Ile Val
225 230 235 240

Phe Gly Val Ala Leu Arg Lys Leu Gly Pro Glu Gly Glu Leu Leu Ile
245 250 255

Arg Phe Phe Asn Ser Phe Asn Glu Ala Thr Met Val Leu Val Ser Trp
260 265 270

Ile Met Trp Tyr Ala Pro Val Gly Ile Met Phe Leu Val Ala Gly Lys
275 280 285

Ile Val Glu Met Glu Asp Val Gly Leu Leu Phe Ala Arg Leu Gly Lys
290 295 300

Tyr Ile Leu Cys Cys Leu Leu Gly His Ala Ile His Gly Leu Leu Val
305 310 315 320

Leu Pro Leu Ile Tyr Phe Leu Phe Thr Arg Lys Asn Pro Tyr Arg Phe
325 330 335

Leu Trp Gly Ile Val Thr Pro Leu Ala Thr Ala Phe Gly Thr Ser Ser
340 345 350

Ser Ser Ala Thr Leu Pro Leu Met Met Lys Cys Val Glu Glu Asn Asn
355 360 365

Gly Val Ala Lys His Ile Ser Arg Phe Ile Leu Pro Ile Gly Ala Thr
370 375 380

Val Asn Met Asp Gly Ala Ala Leu Phe Gln Cys Val Ala Ala Val Phe
385 390 395 400

Ile Ala Gln Leu Ser Gln Gln Ser Leu Asp Phe Val Lys Ile Ile Thr
405 410 415

Ile Leu Val Thr Ala Thr Ala Ser Ser Val Gly Ala Ala Gly Ile Pro
420 425 430

Ala Gly Gly Val Leu Thr Leu Ala Ile Ile Leu Glu Ala Val Asn Leu
435 440 445

Pro Val Asp His Ile Ser Leu Ile Leu Ala Val Asp Trp Leu Val Asp
450 455 460

Arg Ser Cys Thr Val Leu Asn Val Glu Gly Asp Ala Leu Gly Ala Gly
465 470 475 480

Leu Leu Gln Asn Tyr Val Asp Arg Thr Glu Ser Arg Ser Thr Glu Pro
485 490 495

Glu Leu Ile Gln Val Lys Ser Glu Leu Pro Leu Asp Pro Leu Pro Val
500 505 510

Pro Thr Glu Glu Gly Asn Pro Leu Leu Lys His Tyr Arg Gly Pro Ala
515 520 525

Gly Asp Ala Thr Val Ala Ser Glu Lys Glu Ser Val Met
530 535 540

<210> 69
<211> 2445
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (467)..(1441)
<223>

<400> 69
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gcagcccccg acctcccggg ctcaggtgat tctcccgcct cagcaccgcg agcagctagg 180

accacaggcg cgagccactg cgtccggccg gcgggactta tttgtcaggc ggggattggg 240

ttccgccagc ctaaagggag gggtaagcgc cagaatatga atcgccggga agctgggaga 300

aagctccggg aaaccctgag cagccaggtc gcctgctccg cccgctcccg ctcccgatct 360

ctgattgctc ctaactgacg tcactcccgg tctgtccccg cccactcggt gctgccattg 420

gcagtcggtc gtgggtctga gagtcactgg agctaccaga agcatc atg ggg ccc 475
Met Gly Pro
1

tgg gga gag cca gag ctc ctg gtg tgg cgc ccc gag gcg gta gct tca 523
Trp Gly Glu Pro Glu Leu Leu Val Trp Arg Pro Glu Ala Val Ala Ser
5 10 15

gag cct cca gtg cct gtg ggg ctg gag gtg aag ttg ggg gcc ctg gtg 571
Glu Pro Pro Val Pro Val Gly Leu Glu Val Lys Leu Gly Ala Leu Val
20 25 30 35

ctg ctg ctg gtg ctc acc ctc ctc tgc agc ctg gtg ccc atc tgt gtg 619
Leu Leu Leu Val Leu Thr Leu Leu Cys Ser Leu Val Pro Ile Cys Val
40 45 50

ctg cgc cgg cca gga gct aac cat gaa ggc tca gct tcc cgc cag aaa 667
Leu Arg Arg Pro Gly Ala Asn His Glu Gly Ser Ala Ser Arg Gln Lys
55 60 65

gcc ctg agc cta gta agc tgt ttc gcg ggg ggc gtc ttt ttg gcc act 715
Ala Leu Ser Leu Val Ser Cys Phe Ala Gly Gly Val Phe Leu Ala Thr
70 75 80

tgt ctc ctg gac ctg ctg cct gac tac ctg gct gcc ata gat gag gcc 763
Cys Leu Leu Asp Leu Leu Pro Asp Tyr Leu Ala Ala Ile Asp Glu Ala
85 90 95

ctg gca gcc ttg cac gtg acg ctc cag ttc cca ctg caa gag ttc atc 811
Leu Ala Ala Leu His Val Thr Leu Gln Phe Pro Leu Gln Glu Phe Ile
100 105 110 115

ctg gcc atg ggc ttc ttc ctg gtc ctg gtg atg gag cag atc aca ctg 859
Leu Ala Met Gly Phe Phe Leu Val Leu Val Met Glu Gln Ile Thr Leu
120 125 130

gct tac aag gag cag tca ggg ccg tca cct ctg gag gaa aca agg gct 907
Ala Tyr Lys Glu Gln Ser Gly Pro Ser Pro Leu Glu Glu Thr Arg Ala
135 140 145

ctg ctg gga aca gtg aat ggt ggg ccg cag cat tgg cat gat ggg cca 955
Leu Leu Gly Thr Val Asn Gly Gly Pro Gln His Trp His Asp Gly Pro
150 155 160

ggg gtc cca cag gcg agt gga gcc cca gca acc ccc tca gcc ttg cgt 1003
Gly Val Pro Gln Ala Ser Gly Ala Pro Ala Thr Pro Ser Ala Leu Arg
165 170 175

gcc tgt gta ctg gtg ttc tcc ctg gcc ctc cac tcc gtg ttc gag ggg 1051
Ala Cys Val Leu Val Phe Ser Leu Ala Leu His Ser Val Phe Glu Gly
180 185 190 195

ctg gcg gta ggg ctg cag cga gac cgg gct cgg gcc atg gag ctg tgc 1099
Leu Ala Val Gly Leu Gln Arg Asp Arg Ala Arg Ala Met Glu Leu Cys
200 205 210

ctg gct ttg ctg ctc cac aag ggc atc ctg gct gtc agc ctg tcc ctg 1147
Leu Ala Leu Leu Leu His Lys Gly Ile Leu Ala Val Ser Leu Ser Leu
215 220 225

cgg ctg ttg cag agc cac ctt agg gca cag gtg gtg gct ggc tgt ggg 1195
Arg Leu Leu Gln Ser His Leu Arg Ala Gln Val Val Ala Gly Cys Gly
230 235 240

atc ctc ttc tca tgc atg aca cct cta ggc atc ggg ctg ggt gca gct 1243
Ile Leu Phe Ser Cys Met Thr Pro Leu Gly Ile Gly Leu Gly Ala Ala
245 250 255

ctg gca gag tcg gca gga cct ctg cac cag ctg gcc cag tct gtg cta 1291
Leu Ala Glu Ser Ala Gly Pro Leu His Gln Leu Ala Gln Ser Val Leu
260 265 270 275

gag ggc atg gca gct ggc acc ttt ctc tat atc acc ttt ctg gaa atc 1339
Glu Gly Met Ala Ala Gly Thr Phe Leu Tyr Ile Thr Phe Leu Glu Ile
280 285 290

ctg ccc cag gag ctg gcc agt tct gag caa agg atc ctc aag gtc att 1387
Leu Pro Gln Glu Leu Ala Ser Ser Glu Gln Arg Ile Leu Lys Val Ile
295 300 305

ctg ctc cta gca ggc ttt gcc ctg ctc act ggc ctg ctc ttc atc caa 1435
Leu Leu Leu Ala Gly Phe Ala Leu Leu Thr Gly Leu Leu Phe Ile Gln
310 315 320

atc tag ggggcttcaa gagaggggca ggggagattg atgatcaggt gcccctgttc 1491
Ile

tcccttccct cccccagttg tggggaatag gaaggaaagg ggaagggaaa tactgaggac 1551

caaaaagttc tctgggagct aaagatagag cctttggggc tatctgacta atgagaggga 1611

agtgggcaga caagaggctg gccccagtcc caaggaacaa gagatggtca agtcgctaga 1671

gacatatcag gggacattag gattggggaa gacacttgac tgctagaatc agaggttgga 1731

cactatacat aaggacaggc tcacatggga ggctggaggt gggtacccag ctgctgtgga 1791

acgggtatgg acaggtcata aacctagagt cagtgtcctg ttggtcctag cccatttcag 1851

caccctgcca cttggagtgg acccctccta ctcttcttag cgcctaccct catacctatc 1911

tccctcctcc catctcctag gggactggcg ccaaatggtc tctccctgcc aattttggta 1971

tcttctctgg cctctccagt cctgcttact cctctatttt taaagtgcca aacaaatccc 2031

cttcctcttt ctcaaagcac agtaatgtgg cactgagccc tacccagcac ctcagtgaag 2091

ggggcctgct tgctctttat tttggtcccg gatcctgggg tggggcagaa atattttctg 2151

ggctggggta ggaggaaggt tgttgcagcc atctactgct gctgtaccct aggaatatgg 2211

ggacatggac atggtgtccc atgcccagat gataaacact gagctgccaa aacatttttt 2271

taaatacacc cgaggagccc aaggggggaag ggcaatgcct acccccagcg ttatttttgg 2331

ggagggaggg ctgtgcatag ggacatattc tttagaatct attttattaa ctgacctgtt 2391

ttgggacctg ttacccaaat aaaagatgtt tctagaaaaa aaaaaaaaaa aaaa 2445

<210> 70
<211> 324
<212> PRT

<213> Homo sapiens

<400> 70

Met Gly Pro Trp Gly Glu Pro Glu Leu Leu Val Trp Arg Pro Glu Ala
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Val Ala Ser Glu Pro Pro Val Pro Val Gly Leu Glu Val Lys Leu Gly
20 25 30

Ala Leu Val Leu Leu Leu Val Leu Thr Leu Leu Cys Ser Leu Val Pro
35 40 45

Ile Cys Val Leu Arg Arg Pro Gly Ala Asn His Glu Gly Ser Ala Ser
50 55 60

Arg Gln Lys Ala Leu Ser Leu Val Ser Cys Phe Ala Gly Gly Val Phe
65 70 75 80

Leu Ala Thr Cys Leu Leu Asp Leu Leu Pro Asp Tyr Leu Ala Ala Ile
85 90 95

Asp Glu Ala Leu Ala Ala Leu His Val Thr Leu Gln Phe Pro Leu Gln
100 105 110

Glu Phe Ile Leu Ala Met Gly Phe Phe Leu Val Leu Val Met Glu Gln
115 120 125

Ile Thr Leu Ala Tyr Lys Glu Gln Ser Gly Pro Ser Pro Leu Glu Glu
130 135 140

Thr Arg Ala Leu Leu Gly Thr Val Asn Gly Gly Pro Gln His Trp His
145 150 155 160

Asp Gly Pro Gly Val Pro Gln Ala Ser Gly Ala Pro Ala Thr Pro Ser
165 170 175

Ala Leu Arg Ala Cys Val Leu Val Phe Ser Leu Ala Leu His Ser Val
180 185 190

Phe Glu Gly Leu Ala Val Gly Leu Gln Arg Asp Arg Ala Arg Ala Met
195 200 205

Glu Leu Cys Leu Ala Leu Leu Leu His Lys Gly Ile Leu Ala Val Ser
210 215 220

Leu Ser Leu Arg Leu Leu Gln Ser His Leu Arg Ala Gln Val Val Ala
225 230 235 240

Gly Cys Gly Ile Leu Phe Ser Cys Met Thr Pro Leu Gly Ile Gly Leu
245 250 255

Gly Ala Ala Leu Ala Glu Ser Ala Gly Pro Leu His Gln Leu Ala Gln
260 265 270

Ser Val Leu Glu Gly Met Ala Ala Gly Thr Phe Leu Tyr Ile Thr Phe
275 280 285

Leu Glu Ile Leu Pro Gln Glu Leu Ala Ser Ser Glu Gln Arg Ile Leu
290 295 300

Lys Val Ile Leu Leu Leu Ala Gly Phe Ala Leu Leu Thr Gly Leu Leu
305 310 315 320

Phe Ile Gln Ile

<210> 71
<211> 1544
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (301)..(1059)
<223>

<220>
<221> misc_feature
<222> (1358)..(1358)
<223> n = any nucleotide

<220>
<221> misc_feature
<222> (1358)..(1358)
<223> n = a, t, c, or g

<400> 71
gcacgagttg ggaggtgtag cgcggctctg aacgcgctga gggccgttga gtgtcgcagg 60

cggcgagggc gcgagtgagg agcagaccca ggcatcgcgc gccgagaagg ccgggcgtcc 120

ccacactgaa ggtccggaaa ggcgacttcc gggggctttg gcacctggcg gaccctcccg 180

gagcgtcggc acctgaacgc gaggcgctcc attgcgcgtg cgcgttgagg ggcttcccgc 240

acctgatcgc gagaccccaa cggctggtgg cgtcgcctgc gcgtctcggc tgagctggcc 300

atg gcg cag ctg tgc ggg ctg agg cgg agc cgg gcg ttt ctc gcc ctg 348
Met Ala Gln Leu Cys Gly Leu Arg Arg Ser Arg Ala Phe Leu Ala Leu
1 5 10 15

ctg gga tcg ctg ctc ctc tct ggg gtc ctg gcg gcc gac cga gaa cgc 396
Leu Gly Ser Leu Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg
20 25 30

agc atc cac gac ttc tgc ctg gtg tcg aag gtg gtg ggc aga tgc cgg 444
Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
35 40 45

gcc tcc atg cct agg tgg tgg tac aat gtc act gac gga tcc tgc cag 492
Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
50 55 60

ctg ttt gtg tat ggg ggc tgt gac gga aac agc aat aat tac ctg acc 540
Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
65 70 75 80

aag gag gag tgc ctc aag aaa tgt gcc act gtc aca gag aat gcc acg 588
Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
85 90 95

ggt gac ctg gcc acc agc agg aat gca gcg gat tcc tct gtc cca agt 636
Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
100 105 110

gct ccc aga agg cag gat tct gaa gac cac tcc agc gat atg ttc aac 684
Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
115 120 125

tat gaa gaa tac tgc acc gcc aac gca gtc act ggg cct tgc cgt gca 732
Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
130 135 140

tcc ttc cca cgc tgg tac ttt gac gtg gag agg aac tcc tgc aat aac 780
Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
145 150 155 160

ttc atc tat gga ggc tgc cgg ggc aat aag aac agc tac cgc tct gag 828
Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
165 170 175

gag gcc tgc atg ctc cgc tgc ttc cgc cag cag gag aat cct ccc ctg 876
Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
180 185 190

ccc ctt ggc tca aag gtg gtg gtt ctg gcg ggg ctg ttc gtg atg gtg 924
Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
195 200 205

ttg atc ctc ttc ctg gga gcc tcc atg gtc tac ctg atc cgg gtg gca 972
Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
210 215 220

cgg agg aac cag gag cgt gcc ctg cgc acc gtc tgg agc tcc gga gat 1020
Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly Asp
225 230 235 240

gac aag gag cag ctg gtg aag aac aca tat gtc ctg tga ccgccctgtc 1069
Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
245 250

gccaagagga ctggggaagg gaggggagac tatgtgtgag ctttttttaa atagagggat 1129

tgactcggat ttgagtgatc attagggctg aggtctgttt ctctgggagg taggacggct 1189

gcttcctggt ctggcaggga tgggtttgct ttggaaatcc tctaggaggc tcctcctcgc 1249

atggcctgca gtctggcagc agccccgagt tgtttcctcg ctgatcgatt tctttcctcc 1309

aggtagagtt ttctttgctt atgttgaatt ccattgcctc cttttctcna tcacagaagt 1369

gatgttggaa tcgtttcttt tgtttgtctg atttatggtt tttttaagta taaacaaaag 1429

ttttttatta gcattctgaa agaaggaaag taaaatgtac aagtttaata aaaaggggcc 1489

ttccccttta gaataaattt ccagcatgtt gctttcaaaa aaaaaaaaaa aaaaa 1544

<210> 72
<211> 252
<212> PRT
<213> Homo sapiens

<400> 72

Met Ala Gln Leu Cys Gly Leu Arg Arg Ser Arg Ala Phe Leu Ala Leu
1 5 10 15

Leu Gly Ser Leu Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg
20 25 30

Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
35 40 45

Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
50 55 60

Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
65 70 75 80

Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
85 90 95

Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
100 105 110

Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
115 120 125

Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
130 135 140

Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
145 150 155 160

Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
165 170 175

Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
180 185 190

Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
195 200 205

Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
210 215 220

Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly Asp
225 230 235 240

Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
245 250

<210> 73
<211> 2380
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (135)..(1043)
<223>

<400> 73
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gaggaagagg aggaggagga agaggggagc acaaaggatc caggtctccc gacgggaggt 120

taataccaag aacc atg tgt gcc gag cgg ctg ggc cag ttc atg acc ctg 170
Met Cys Ala Glu Arg Leu Gly Gln Phe Met Thr Leu
1 5 10

gct ttg gtg ttg gcc acc ttt gac ccg gcg cgg ggg acc gac gcc acc 218
Ala Leu Val Leu Ala Thr Phe Asp Pro Ala Arg Gly Thr Asp Ala Thr
15 20 25

aac cca ccc gag ggt ccc caa gac agg agc tcc cag cag aaa ggc cgc 266
Asn Pro Pro Glu Gly Pro Gln Asp Arg Ser Ser Gln Gln Lys Gly Arg
30 35 40

ctg tcc ctg cag aat aca gcg gag atc cag cac tgt ttg gtc aac gct 314
Leu Ser Leu Gln Asn Thr Ala Glu Ile Gln His Cys Leu Val Asn Ala
45 50 55 60

ggc gat gtg ggg tgt ggc gtg ttt gaa tgt ttc gag aac aac tct tgt 362
Gly Asp Val Gly Cys Gly Val Phe Glu Cys Phe Glu Asn Asn Ser Cys
65 70 75

gag att cgg ggc tta cat ggg att tgc atg act ttt ctg cac aac gct 410
Glu Ile Arg Gly Leu His Gly Ile Cys Met Thr Phe Leu His Asn Ala
80 85 90

gga aaa ttt gat gcc cag ggc aag tca ttc atc aaa gac gcc ttg aaa 458
Gly Lys Phe Asp Ala Gln Gly Lys Ser Phe Ile Lys Asp Ala Leu Lys
95 100 105

tgt aag gcc cac gct ctg cgg cac agg ttc ggc tgc ata agc cgg aag 506
Cys Lys Ala His Ala Leu Arg His Arg Phe Gly Cys Ile Ser Arg Lys
110 115 120

tgc ccg gcc atc agg gaa atg gtg tcc cag ttg cag cgg gaa tgc tac 554

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Cys Pro Ala Ile Arg Glu Met Val Ser Gln Leu Gln Arg Glu Cys Tyr
125                 130                 135                 140

ctc aag cac gac ctg tgc gcg gct gcc cag gag aac acc cgg gtg ata      602
Leu Lys His Asp Leu Cys Ala Ala Ala Gln Glu Asn Thr Arg Val Ile
                145                 150                 155

gtg gag atg atc cat ttc aag gac ttg ctg ctg cac gaa ccc tac gtg      650
Val Glu Met Ile His Phe Lys Asp Leu Leu Leu His Glu Pro Tyr Val
            160                 165                 170

gac ctc gtg aac ttg ctg ctg acc tgt ggg gag gag gtg aag gag gcc      698
Asp Leu Val Asn Leu Leu Leu Thr Cys Gly Glu Glu Val Lys Glu Ala
        175                 180                 185

atc acc cac agc gtg cag gtt cag tgt gag cag aac tgg gga agc ctg      746
Ile Thr His Ser Val Gln Val Gln Cys Glu Gln Asn Trp Gly Ser Leu
    190                 195                 200

tgc tcc atc ttg agc ttc tgc acc tcg gcc atc cag aag cct ccc acg      794
Cys Ser Ile Leu Ser Phe Cys Thr Ser Ala Ile Gln Lys Pro Pro Thr
205                 210                 215                 220

gcg ccc ccc gag cgc cag ccc cag gtg gac aga acc aag ctc tcc agg      842
Ala Pro Pro Glu Arg Gln Pro Gln Val Asp Arg Thr Lys Leu Ser Arg
                225                 230                 235

gcc cac cac ggg gaa gca gga cat cac ctc cca gag ccc agc agt agg      890
Ala His His Gly Glu Ala Gly His His Leu Pro Glu Pro Ser Ser Arg
            240                 245                 250

gag act ggc cga ggt gcc aag ggt gag cga ggt agc aag agc cac cca      938
Glu Thr Gly Arg Gly Ala Lys Gly Glu Arg Gly Ser Lys Ser His Pro
        255                 260                 265

aac gcc cat gcc cga ggc aga gtc ggg ggc ctt ggg gct cag gga cct      986
Asn Ala His Ala Arg Gly Arg Val Gly Gly Leu Gly Ala Gln Gly Pro
    270                 275                 280

tcc gga agc agc gag tgg gaa gac gaa cag tct gag tat tct gat atc     1034
Ser Gly Ser Ser Glu Trp Glu Asp Glu Gln Ser Glu Tyr Ser Asp Ile
285                 290                 295                 300

cgg agg tga aatgaaaggc ctggccacga aatctttcct ccacgccgtc              1083
Arg Arg

cattttctta tctatggaca ttccaaaaca tttaccatta gagaggggag atgtcacacg    1143

caggattctg tggggactgt ggacttcatc gaggtgtgtg ttcgcggaac ggacaggtga    1203

gatggagacc cctggggccg tggggtctca ggggtgcctg gtgaattctg cacttacacg    1263

tactcaaggg agcgcgcccg cgttatcctc gtacctttgt cttctttcca tctgtggagt    1323

cagtgggtgt cggccgctct gttgtggggg aggtgaacca gggaggggca gggcaaggca    1383

gggcccccag agctgggcca cacagtgggt gctgggcctc gccccgaagc ttctggtgca    1443

gcagcctctg gtgctgtctc cgcggaagtc agggcggctg gattccagga caggagtgaa    1503

tgtaaaaata aatatcgctt agaatgcagg agaagggtgg agaggaggca ggggccgagg    1563

gggtgcttgg tgccaaactg aaattcagtt tcttgtgtgg ggccttgcgg ttcagagctc    1623

ttggcgaggg tggagggagg agtgtcattt ctatgtgtaa tttctgagcc attgtactgt    1683

ctgggctggg ggggacactg tccaagggag tggcccctat gagtttatat tttaaccact    1743

gcttcaaatc tcgatttcac ttttttttatt tatccagtta tatctacata tctgtcatct    1803

aaataaatgg ctttcaaaca aagcaactgg gtcattaaaa ccagctcaaa gggggtttaa    1863

aaaaaaaaaa accagcccat cctttgaggc tgatttttct ttttttaag ttctatttta     1923

aaagctatca aacagcgaca tagccataca tctgactgcc tgacatggac tcctgcccac    1983

ttgggggaaa ccttataccc agaggaaaat acacacctgg ggagtacatt tgacaaattt    2043

cccttaggat ttcgttatct caccttgacc ctcagccaag attggtaaag ctgcgtcctg    2103
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gcgattccag gagacccagc tggaaacctg gcttctccat gtgaggggat gggaaaggaa 2163

agaagagaat gaagactact tagtaattcc catcaggaaa tgctgacctt ttacataaaa 2223

tcaaggagac tgctgaaaat ctctaaggga caggattttc cagatcctaa ttggaaattt 2283

agcaataagg agaggagtcc aaggggacaa ataaaggcag agagagagag agagagaggg 2343

agaggaagaa aagagagaga gaaaagagcc tcgtgcc 2380

<210> 74
<211> 302
<212> PRT
<213> Homo sapiens

<400> 74

Met Cys Ala Glu Arg Leu Gly Gln Phe Met Thr Leu Ala Leu Val Leu
1 5 10 15

Ala Thr Phe Asp Pro Ala Arg Gly Thr Asp Ala Thr Asn Pro Pro Glu
20 25 30

Gly Pro Gln Asp Arg Ser Ser Gln Gln Lys Gly Arg Leu Ser Leu Gln
35 40 45

Asn Thr Ala Glu Ile Gln His Cys Leu Val Asn Ala Gly Asp Val Gly
50 55 60

Cys Gly Val Phe Glu Cys Phe Glu Asn Asn Ser Cys Glu Ile Arg Gly
65 70 75 80

Leu His Gly Ile Cys Met Thr Phe Leu His Asn Ala Gly Lys Phe Asp
85 90 95

Ala Gln Gly Lys Ser Phe Ile Lys Asp Ala Leu Lys Cys Lys Ala His
100 105 110

Ala Leu Arg His Arg Phe Gly Cys Ile Ser Arg Lys Cys Pro Ala Ile
115 120 125

Arg Glu Met Val Ser Gln Leu Gln Arg Glu Cys Tyr Leu Lys His Asp
130 135 140

Leu Cys Ala Ala Ala Gln Glu Asn Thr Arg Val Ile Val Glu Met Ile
145 150 155 160

His Phe Lys Asp Leu Leu Leu His Glu Pro Tyr Val Asp Leu Val Asn
165 170 175

Leu Leu Leu Thr Cys Gly Glu Glu Val Lys Glu Ala Ile Thr His Ser
180 185 190

Val Gln Val Gln Cys Glu Gln Asn Trp Gly Ser Leu Cys Ser Ile Leu
195 200 205

Ser Phe Cys Thr Ser Ala Ile Gln Lys Pro Pro Thr Ala Pro Pro Glu
210 215 220

Arg Gln Pro Gln Val Asp Arg Thr Lys Leu Ser Arg Ala His His Gly
225 230 235 240

Glu Ala Gly His His Leu Pro Glu Pro Ser Ser Arg Glu Thr Gly Arg
245 250 255

Gly Ala Lys Gly Glu Arg Gly Ser Lys Ser His Pro Asn Ala His Ala
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Arg Gly Arg Val Gly Gly Leu Gly Ala Gln Gly Pro Ser Gly Ser Ser
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Glu Trp Glu Asp Glu Gln Ser Glu Tyr Ser Asp Ile Arg Arg
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gctctctcgc gcccagtcct cctccctggt tctcctcagc cgctgtcgga ggagagcacc 180

cggagacgcg ggctgcagtc gcggcggctt ctccccgcct gggcggccgc gccgctgggc 240

aggtgctgag cgcccctaga gcctcccttg ccgcctccct cctctgcccg gccgcagcag 300

tgcacatggg gtgttggagg tagatgggct cccggcccgg gaggcggcgg tggatgcggc 360

gctgggcaga agcagccgcc gattccagct gccccgcgcg ccccgggcgc ccctgcgagt 420

ccccggttca gcc atg ggg acc tct ccg agc agc agc acc gcc ctc gcc 469
Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala
1 5 10

tcc tgc agc cgc atc gcc cgc cga gcc aca gcc acg atg atc gcg ggc 517
Ser Cys Ser Arg Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly
15 20 25

tcc ctt ctc ctg ctt gga ttc ctt agc acc acc aca gct cag cca gaa 565
Ser Leu Leu Leu Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu
30 35 40

cag aag gcc tcg aat ctc att ggc aca tac cgc cat gtt gac cgt gcc 613
Gln Lys Ala Ser Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala
45 50 55 60

acc ggc cag gtg cta acc tgt gac aag tgt cca gca gga acc tat gtc 661
Thr Gly Gln Val Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val
65 70 75

tct gag cat tgt acc aac aca agc ctg cgc gtc tgc agc agt tgc cct 709
Ser Glu His Cys Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro
80 85 90

gtg ggg acc ttt acc agg cat gag aat ggc ata gag aaa tgc cat gac 757
Val Gly Thr Phe Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp
95 100 105

tgt agt cag cca tgc cca tgg cca atg att gag aaa tta cct tgt gct 805
Cys Ser Gln Pro Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala
110 115 120

gcc ttg act gac cga gaa tgc act tgc cca cct ggc atg ttc cag tct 853
Ala Leu Thr Asp Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser
125 130 135 140

aac gct acc tgt gcc ccc cat acg gtg tgt cct gtg ggt tgg ggt gtg 901
Asn Ala Thr Cys Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val
145 150 155

cgg aag aaa ggg aca gag act gag gat gtg cgg tgt aag cag tgt gct 949
Arg Lys Lys Gly Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala

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                160                 165                 170

cgg ggt acc ttc tca gat gtg cct tct agt gtg atg aaa tgc aaa gca      997
Arg Gly Thr Phe Ser Asp Val Pro Ser Ser Val Met Lys Cys Lys Ala
        175                 180                 185

tac aca gac tgt ctg agt cag aac ctg gtg gtg atc aag ccg ggg acc     1045
Tyr Thr Asp Cys Leu Ser Gln Asn Leu Val Val Ile Lys Pro Gly Thr
    190                 195                 200

aag gag aca gac aac gtc tgt ggc aca ctc ccg tcc ttc tcc agc tcc     1093
Lys Glu Thr Asp Asn Val Cys Gly Thr Leu Pro Ser Phe Ser Ser Ser
205                 210                 215                 220

acc tca cct tcc cct ggc aca gcc atc ttt cca cgc cct gag cac atg     1141
Thr Ser Pro Ser Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met
                225                 230                 235

gaa acc cat gaa gtc cct tcc tcc act tat gtt ccc aaa ggc atg aac     1189
Glu Thr His Glu Val Pro Ser Ser Thr Tyr Val Pro Lys Gly Met Asn
            240                 245                 250

tca aca gaa tcc aac tct tct gcc tct gtt aga cca aag gta ctg agt     1237
Ser Thr Glu Ser Asn Ser Ser Ala Ser Val Arg Pro Lys Val Leu Ser
        255                 260                 265

agc atc cag gaa ggg aca gtc cct gac aac aca agc tca gca agg ggg     1285
Ser Ile Gln Glu Gly Thr Val Pro Asp Asn Thr Ser Ser Ala Arg Gly
    270                 275                 280

aag gaa gac gtg aac aag acc ctc cca aac ctt cag gta gtc aac cac     1333
Lys Glu Asp Val Asn Lys Thr Leu Pro Asn Leu Gln Val Val Asn His
285                 290                 295                 300

cag caa ggc ccc cac cac aga cac atc ctg aag ctg ctg ccg tcc atg     1381
Gln Gln Gly Pro His His Arg His Ile Leu Lys Leu Leu Pro Ser Met
                305                 310                 315

gag gcc act ggg ggc gag aag tcc agc acg ccc atc aag ggc ccc aag     1429
Glu Ala Thr Gly Gly Glu Lys Ser Ser Thr Pro Ile Lys Gly Pro Lys
            320                 325                 330

agg gga cat cct aga cag aac cta cac aag cat ttt gac atc aat gag     1477
Arg Gly His Pro Arg Gln Asn Leu His Lys His Phe Asp Ile Asn Glu
        335                 340                 345

cat ttg ccc tgg atg att gtg ctt ttc ctg ctg ctg gtg ctt gtg gtg     1525
His Leu Pro Trp Met Ile Val Leu Phe Leu Leu Leu Val Leu Val Val
    350                 355                 360

att gtg gtg tgc agt atc cgg aaa agc tcg agg act ctg aaa aag ggg     1573
Ile Val Val Cys Ser Ile Arg Lys Ser Ser Arg Thr Leu Lys Lys Gly
365                 370                 375                 380

ccc cgg cag gat ccc agt gcc att gtg gaa aag gca ggg ctg aag aaa     1621
Pro Arg Gln Asp Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys
                385                 390                 395

tcc atg act cca acc cag aac cgg gag aaa tgg atc tac tac tgc aat     1669
Ser Met Thr Pro Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn
            400                 405                 410

ggc cat ggt atc gat atc ctg aag ctt gta gca gcc caa gtg gga agc     1717
Gly His Gly Ile Asp Ile Leu Lys Leu Val Ala Ala Gln Val Gly Ser
        415                 420                 425

cag tgg aaa gat atc tat cag ttt ctt tgc aat gcc agt gag agg gag     1765
Gln Trp Lys Asp Ile Tyr Gln Phe Leu Cys Asn Ala Ser Glu Arg Glu
    430                 435                 440

gtt gct gct ttc tcc aat ggg tac aca gcc gac cac gag cgg gcc tac     1813
Val Ala Ala Phe Ser Asn Gly Tyr Thr Ala Asp His Glu Arg Ala Tyr
445                 450                 455                 460

gca gct ctg cag cac tgg acc atc cgg ggc ccc gag gcc agc ctc gcc     1861
Ala Ala Leu Gln His Trp Thr Ile Arg Gly Pro Glu Ala Ser Leu Ala
                465                 470                 475

cag cta att agc gcc ctg cgc cag cac cgg aga aac gat gtt gtg gag     1909
Gln Leu Ile Ser Ala Leu Arg Gln His Arg Arg Asn Asp Val Val Glu
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                480                 485                 490

aag att cgt ggg ctg atg gaa gac acc acc cag ctg gaa act gac aaa      1957
Lys Ile Arg Gly Leu Met Glu Asp Thr Thr Gln Leu Glu Thr Asp Lys
        495                 500                 505

cta gct ctc ccg atg agc ccc agc ccg ctt agc ccg agc ccc atc ccc      2005
Leu Ala Leu Pro Met Ser Pro Ser Pro Leu Ser Pro Ser Pro Ile Pro
    510                 515                 520

agc ccc aac gcg aaa ctt gag aat tcc gct ctc ctg acg gtg gag cct      2053
Ser Pro Asn Ala Lys Leu Glu Asn Ser Ala Leu Leu Thr Val Glu Pro
525                 530                 535                 540

tcc cca cag gac aag aac aag ggc ttc ttc gtg gat gag tcg gag ccc      2101
Ser Pro Gln Asp Lys Asn Lys Gly Phe Phe Val Asp Glu Ser Glu Pro
                545                 550                 555

ctt ctc cgc tgt gac tct aca tcc agc ggc tcc tcc gcg ctg agc agg      2149
Leu Leu Arg Cys Asp Ser Thr Ser Ser Gly Ser Ser Ala Leu Ser Arg
            560                 565                 570

aac ggt tcc ttt att acc aaa gaa aag aag gac aca gtg ttg cgg cag      2197
Asn Gly Ser Phe Ile Thr Lys Glu Lys Lys Asp Thr Val Leu Arg Gln
        575                 580                 585

gta cgc ctg gac ccc tgt gac ttg cag cct atc ttt gat gac atg ctc      2245
Val Arg Leu Asp Pro Cys Asp Leu Gln Pro Ile Phe Asp Asp Met Leu
    590                 595                 600

cac ttt cta aat cct gag gag ctg cgg gtg att gaa gag att ccc cag      2293
His Phe Leu Asn Pro Glu Glu Leu Arg Val Ile Glu Glu Ile Pro Gln
605                 610                 615                 620

gct gag gac aaa cta gac cgg cta ttc gaa att att gga gtc aag agc      2341
Ala Glu Asp Lys Leu Asp Arg Leu Phe Glu Ile Ile Gly Val Lys Ser
                625                 630                 635

cag gaa gcc agc cag acc ctc ctg gac tct gtt tat agc cat ctt cct      2389
Gln Glu Ala Ser Gln Thr Leu Leu Asp Ser Val Tyr Ser His Leu Pro
            640                 645                 650

gac ctg ctg tag aacataggga tactgcattc tggaaattac tcaatttagt          2441
Asp Leu Leu
        655

ggcagggtgg ttttttaatt ttcttctgtt tctgattttt gttgtttggg gtgtgtgtgt   2501

gtgtttgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt ttaacagaga atatggccag   2561

tgcttgagtt ctttctcctt ctctctctct ctttttttta taaataactc ttctgggaag   2621

ttggtttata agcctttgcc aggtgtaact gttgtgaaat acccaccact aaagtttttt   2681

aagttccata ttttctccat ttgccttct tatgtatttt caagattatt ctgtgcactt   2741

taaatttact taacttacca taaatgcagt gtgacttttc ccacacactg gattgtgagg   2801

ctcttaactt cttaaaagta taatggcatc ttgtgaatcc tataagcagt ctttatgtct   2861

cttaacattc acacctactt tttaaaaaca aatattatta ctatttttat tattgtttgt   2921

cctttataaa ttttcttaaa gattaagaaa atttaagacc ccattgagtt actgtaatgc   2981

aattcaactt tgagttatct tttaaatatg tcttgtatag ttcatattca tggctgaaac   3041

ttgaccacac tattgctgat tgtatggttt tcacctggac accgtgtaga atgcttgatt   3101

acttgtactc ttcttatgct aatatgctct gggctggaga aatgaaatcc tcaagccatc   3161

aggatttgct atttaagtgg cttgacaact gggccaccaa agaacttgaa cttcaccttt   3221

taggatttga gctgttctgg aacacattgc tgcactttgg aaagtcaaaa tcaagtgcca   3281

gtggcgccct ttccatagag aatttgccca gctttgcttt aaaagatgtc ttgtttttta   3341

tatacacata atcaataggt ccaatctgct ctcaaggcct tggtcctggt gggattcctt   3401

caccaattac tttaattaaa aatggctgca actgtaagaa cccttgtctg atatatttgc   3461
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aactatgctc ccatttacaa atgtaccttc taatgctcag ttgccaggtt ccaatgcaaa 3521

ggtggcgtgg actccctttg tgtgggtggg gtttgtgggt agtggtgaag gaccgatatc 3581

agaaaaatgc cttcaagtgt actaatttat taataaacat taggtgtttg ttaaaaaaaa 3641

aaaaaaaaaa aaaaaaaaaa a 3662

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Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu
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Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser
35 40 45

Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val
50 55 60

Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
65 70 75 80

Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe
85 90 95

Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro
100 105 110

Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp
115 120 125

Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys
130 135 140

Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
145 150 155 160

Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe
165 170 175

Ser Asp Val Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys
180 185 190

Leu Ser Gln Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp
195 200 205

Asn Val Cys Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser
210 215 220

Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu
225 230 235 240

Val Pro Ser Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser
245 250 255

Asn Ser Ser Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu
260 265 270

Gly Thr Val Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val
275 280 285

Asn Lys Thr Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro
290 295 300

His His Arg His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly
305 310 315 320

Gly Glu Lys Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro
325 330 335

Arg Gln Asn Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp
340 345 350

Met Ile Val Leu Phe Leu Leu Leu Val Leu Val Val Ile Val Val Cys
355 360 365

Ser Ile Arg Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp
370 375 380

Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro
385 390 395 400

Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Ile
405 410 415

Asp Ile Leu Lys Leu Val Ala Ala Gln Val Gly Ser Gln Trp Lys Asp
420 425 430

Ile Tyr Gln Phe Leu Cys Asn Ala Ser Glu Arg Glu Val Ala Ala Phe
435 440 445

Ser Asn Gly Tyr Thr Ala Asp His Glu Arg Ala Tyr Ala Ala Leu Gln
450 455 460

His Trp Thr Ile Arg Gly Pro Glu Ala Ser Leu Ala Gln Leu Ile Ser
465 470 475 480

Ala Leu Arg Gln His Arg Arg Asn Asp Val Val Glu Lys Ile Arg Gly
485 490 495

Leu Met Glu Asp Thr Thr Gln Leu Glu Thr Asp Lys Leu Ala Leu Pro
500 505 510

Met Ser Pro Ser Pro Leu Ser Pro Ser Pro Ile Pro Ser Pro Asn Ala
515 520 525

Lys Leu Glu Asn Ser Ala Leu Leu Thr Val Glu Pro Ser Pro Gln Asp
530 535 540

Lys Asn Lys Gly Phe Phe Val Asp Glu Ser Glu Pro Leu Leu Arg Cys
545 550 555 560

Asp Ser Thr Ser Ser Gly Ser Ser Ala Leu Ser Arg Asn Gly Ser Phe
565 570 575

Ile Thr Lys Glu Lys Lys Asp Thr Val Leu Arg Gln Val Arg Leu Asp
580 585 590

Pro Cys Asp Leu Gln Pro Ile Phe Asp Asp Met Leu His Phe Leu Asn
595 600 605

Pro Glu Glu Leu Arg Val Ile Glu Glu Ile Pro Gln Ala Glu Asp Lys
610 615 620

Leu Asp Arg Leu Phe Glu Ile Ile Gly Val Lys Ser Gln Glu Ala Ser
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Gln Thr Leu Leu Asp Ser Val Tyr Ser His Leu Pro Asp Leu Leu
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Met Arg Ala Leu
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tgg gtg ctg ggc ctc tgc tgc gtc ctg ctg acc ttc ggg tcg gtc aga 165
Trp Val Leu Gly Leu Cys Cys Val Leu Leu Thr Phe Gly Ser Val Arg
5 10 15 20

gct gac gat gaa gtt gat gtg gat ggt aca gta gaa gag gat ctg ggt 213
Ala Asp Asp Glu Val Asp Val Asp Gly Thr Val Glu Glu Asp Leu Gly
25 30 35

aaa agt aga gaa gga tca agg acg gat gat gaa gta gta cag aga gag 261
Lys Ser Arg Glu Gly Ser Arg Thr Asp Asp Glu Val Val Gln Arg Glu
40 45 50

gaa gaa gct att cag ttg gat gga tta aat gca tca caa ata aga gaa 309
Glu Glu Ala Ile Gln Leu Asp Gly Leu Asn Ala Ser Gln Ile Arg Glu
55 60 65

ctt aga gag aag tcg gaa aag ttt gcc ttc caa gcc gaa gtt aac aga 357
Leu Arg Glu Lys Ser Glu Lys Phe Ala Phe Gln Ala Glu Val Asn Arg
70 75 80

atg atg aaa ctt atc atc aat tca ttg tat aaa aat aaa gag att ttc 405
Met Met Lys Leu Ile Ile Asn Ser Leu Tyr Lys Asn Lys Glu Ile Phe
85 90 95 100

ctg aga gaa ctg att tca aat gct tct gat gct tta gat aag ata agg 453
Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu Asp Lys Ile Arg
105 110 115

cta ata tca ctg act gat gaa aat gct ctt tct gga aat gag gaa cta 501
Leu Ile Ser Leu Thr Asp Glu Asn Ala Leu Ser Gly Asn Glu Glu Leu
120 125 130

aca gtc aaa att aag tgt gat aag gag aag aac ctg ctg cat gtc aca 549
Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu Leu His Val Thr
135 140 145

gac acc ggt gta gga atg acc aga gaa gag ttg gtt aaa aac ctt ggt 597
Asp Thr Gly Val Gly Met Thr Arg Glu Glu Leu Val Lys Asn Leu Gly
150 155 160

acc ata gcc aaa tct ggg aca agc gag ttt tta aac aaa atg act gaa 645
Thr Ile Ala Lys Ser Gly Thr Ser Glu Phe Leu Asn Lys Met Thr Glu
165 170 175 180

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gca cag gaa gat ggc cag tca act tct gaa ttg att ggc cag ttt ggt      693
Ala Gln Glu Asp Gly Gln Ser Thr Ser Glu Leu Ile Gly Gln Phe Gly
                185                 190                 195

gtc ggt ttc tat tcc gcc ttc ctt gta gca gat aag gtt att gtc act      741
Val Gly Phe Tyr Ser Ala Phe Leu Val Ala Asp Lys Val Ile Val Thr
            200                 205                 210

tca aaa cac aac aac gat acc cag cac atc tgg gag tct gac tcc aat      789
Ser Lys His Asn Asn Asp Thr Gln His Ile Trp Glu Ser Asp Ser Asn
        215                 220                 225

gaa ttt tct gta att gct gac cca aga gga aac act cta gga cgg gga      837
Glu Phe Ser Val Ile Ala Asp Pro Arg Gly Asn Thr Leu Gly Arg Gly
    230                 235                 240

acg aca att acc ctt gtc tta aaa gaa gaa gca tct gat tac ctt gaa      885
Thr Thr Ile Thr Leu Val Leu Lys Glu Glu Ala Ser Asp Tyr Leu Glu
245                 250                 255                 260

ttg gat aca att aaa aat ctc gtc aaa aaa tat tca cag ttc ata aac      933
Leu Asp Thr Ile Lys Asn Leu Val Lys Lys Tyr Ser Gln Phe Ile Asn
                265                 270                 275

ttt cct att tat gta tgg agc agc aag act gaa act gtt gag gag ccc      981
Phe Pro Ile Tyr Val Trp Ser Ser Lys Thr Glu Thr Val Glu Glu Pro
            280                 285                 290

atg gag gaa gaa gaa gca gcc aaa gaa gag aaa gaa gaa tct gat gat     1029
Met Glu Glu Glu Glu Ala Ala Lys Glu Glu Lys Glu Glu Ser Asp Asp
        295                 300                 305

gaa gct gca gta gag gaa gaa gaa gaa gaa aag aaa cca aag act aaa     1077
Glu Ala Ala Val Glu Glu Glu Glu Glu Glu Lys Lys Pro Lys Thr Lys
    310                 315                 320

aaa gtt gaa aaa act gtc tgg gac tgg gaa ctt atg aat gat atc aaa     1125
Lys Val Glu Lys Thr Val Trp Asp Trp Glu Leu Met Asn Asp Ile Lys
325                 330                 335                 340

cca ata tgg cag aga cca tca aaa gaa gta gaa gaa gat gaa tac aaa     1173
Pro Ile Trp Gln Arg Pro Ser Lys Glu Val Glu Glu Asp Glu Tyr Lys
                345                 350                 355

gct ttc tac aaa tca ttt tca aag gaa agt gat gac ccc atg gct tat     1221
Ala Phe Tyr Lys Ser Phe Ser Lys Glu Ser Asp Asp Pro Met Ala Tyr
            360                 365                 370

att cac ttt act gct gaa ggg gaa gtt acc ttc aaa tca att tta ttt     1269
Ile His Phe Thr Ala Glu Gly Glu Val Thr Phe Lys Ser Ile Leu Phe
        375                 380                 385

gta ccc aca tct gct cca cgt ggt ctg ttt gac gaa tat gga tct aaa     1317
Val Pro Thr Ser Ala Pro Arg Gly Leu Phe Asp Glu Tyr Gly Ser Lys
    390                 395                 400

aag agc gat tac att aag ctc tat gtg cgc cgt gta ttc atc aca gac     1365
Lys Ser Asp Tyr Ile Lys Leu Tyr Val Arg Arg Val Phe Ile Thr Asp
405                 410                 415                 420

gac ttc cat gat atg atg cct aaa tac ctc aat ttt gtc aag ggt gtg     1413
Asp Phe His Asp Met Met Pro Lys Tyr Leu Asn Phe Val Lys Gly Val
                425                 430                 435

gtg gac tca gat gat ctc ccc ttg aat gtt tcc cgc gag act ctt cag     1461
Val Asp Ser Asp Asp Leu Pro Leu Asn Val Ser Arg Glu Thr Leu Gln
            440                 445                 450

caa cat aaa ctg ctt aag gtg att agg aag aag ctt gtt cgt aaa acg     1509
Gln His Lys Leu Leu Lys Val Ile Arg Lys Lys Leu Val Arg Lys Thr
        455                 460                 465

ctg gac atg atc aag aag att gct gat gat aaa tac aat gat act ttt     1557
Leu Asp Met Ile Lys Lys Ile Ala Asp Asp Lys Tyr Asn Asp Thr Phe
    470                 475                 480

tgg aaa gaa ttt ggt acc aac atc aag ctt ggt gtg att gaa gac cac     1605
Trp Lys Glu Phe Gly Thr Asn Ile Lys Leu Gly Val Ile Glu Asp His
485                 490                 495                 500
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tcg aat cga aca cgt ctt gct aaa ctt ctt agg ttc cag tct tct cat      1653
Ser Asn Arg Thr Arg Leu Ala Lys Leu Leu Arg Phe Gln Ser Ser His
                505                 510                 515

cat cca act gac att act agc cta gac cag tat gtg gaa aga atg aag      1701
His Pro Thr Asp Ile Thr Ser Leu Asp Gln Tyr Val Glu Arg Met Lys
            520                 525                 530

gaa aaa caa gac aaa atc tac ttc atg gct ggg tcc agc aga aaa gag      1749
Glu Lys Gln Asp Lys Ile Tyr Phe Met Ala Gly Ser Ser Arg Lys Glu
        535                 540                 545

gct gaa tct tct cca ttt gtt gag cga ctt ctg aaa aag ggc tat gaa      1797
Ala Glu Ser Ser Pro Phe Val Glu Arg Leu Leu Lys Lys Gly Tyr Glu
    550                 555                 560

gtt att tac ctc aca gaa cct gtg gat gaa tac tgt att cag gcc ctt      1845
Val Ile Tyr Leu Thr Glu Pro Val Asp Glu Tyr Cys Ile Gln Ala Leu
565                 570                 575                 580

ccc gaa ttt gat ggg aag agg ttc cag aat gtt gcc aag gaa gga gtg      1893
Pro Glu Phe Asp Gly Lys Arg Phe Gln Asn Val Ala Lys Glu Gly Val
                585                 590                 595

aag ttc gat gaa agt gag aaa act aag gag agt cgt gaa gca gtt gag      1941
Lys Phe Asp Glu Ser Glu Lys Thr Lys Glu Ser Arg Glu Ala Val Glu
            600                 605                 610

aaa gaa ttt gag cct ctg ctg aat tgg atg aaa gat aaa gcc ctt aag      1989
Lys Glu Phe Glu Pro Leu Leu Asn Trp Met Lys Asp Lys Ala Leu Lys
        615                 620                 625

gac aag att gaa aag gct gtg gtg tct cag cgc ctg aca gaa tct ccg      2037
Asp Lys Ile Glu Lys Ala Val Val Ser Gln Arg Leu Thr Glu Ser Pro
    630                 635                 640

tgt gct ttg gtg gcc agc cag tac gga tgg tct ggc aac atg gag aga      2085
Cys Ala Leu Val Ala Ser Gln Tyr Gly Trp Ser Gly Asn Met Glu Arg
645                 650                 655                 660

atc atg aaa gca caa gcg tac caa acg ggc aag gac atc tct aca aat      2133
Ile Met Lys Ala Gln Ala Tyr Gln Thr Gly Lys Asp Ile Ser Thr Asn
                665                 670                 675

tac tat gcg agt cag aag aaa aca ttt gaa att aat ccc aga cac ccg      2181
Tyr Tyr Ala Ser Gln Lys Lys Thr Phe Glu Ile Asn Pro Arg His Pro
            680                 685                 690

ctg atc aga gac atg ctt cga cga att aag gaa gat gaa gat gat aaa      2229
Leu Ile Arg Asp Met Leu Arg Arg Ile Lys Glu Asp Glu Asp Asp Lys
        695                 700                 705

aca gtt ttg gat ctt gct gtg gtt ttg ttt gaa aca gca acg ctt cgg      2277
Thr Val Leu Asp Leu Ala Val Val Leu Phe Glu Thr Ala Thr Leu Arg
    710                 715                 720

tca ggg tat ctt tta cca gac act aaa gca tat gga gat aga ata gaa      2325
Ser Gly Tyr Leu Leu Pro Asp Thr Lys Ala Tyr Gly Asp Arg Ile Glu
725                 730                 735                 740

aga atg ctt cgc ctc agt ttg aac att gac cct gat gca aag gtg gaa      2373
Arg Met Leu Arg Leu Ser Leu Asn Ile Asp Pro Asp Ala Lys Val Glu
                745                 750                 755

gaa gag ccc gaa gaa gaa cct gaa gag aca gca gaa gac aca aca gaa      2421
Glu Glu Pro Glu Glu Glu Pro Glu Glu Thr Ala Glu Asp Thr Thr Glu
            760                 765                 770

gac aca gag caa gac gaa gat gaa gaa atg gat gtg gga aca gat gaa      2469
Asp Thr Glu Gln Asp Glu Asp Glu Glu Met Asp Val Gly Thr Asp Glu
        775                 780                 785

gaa gaa gaa aca gca aag gaa tct aca gct gaa aaa gat gaa ttg taa      2517
Glu Glu Glu Thr Ala Lys Glu Ser Thr Ala Glu Lys Asp Glu Leu
    790                 795                 800

attatactct caccatttgg atcctgtgtg gagagggaat gtgaaattta catcatttct   2577

ttttgggaga gacttgtttt ggatgccccc taatcccctt ctcccctgca ctgtaaaatg   2637
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tgggattatg ggtcacagga aaaagtgggt tttttagttg aatttttttt aacattcctc 2697

atgaatgtaa atttgtacta tttaactgac tattcttgat gtaaaatctt gtcatgtgta 2757

taaaaataaa aaagatccca aat 2780

<210> 78
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<212> PRT
<213> Homo sapiens

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Met Arg Ala Leu Trp Val Leu Gly Leu Cys Cys Val Leu Leu Thr Phe
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Gly Ser Val Arg Ala Asp Asp Glu Val Asp Val Asp Gly Thr Val Glu
20 25 30

Glu Asp Leu Gly Lys Ser Arg Glu Gly Ser Arg Thr Asp Asp Glu Val
35 40 45

Val Gln Arg Glu Glu Glu Ala Ile Gln Leu Asp Gly Leu Asn Ala Ser
50 55 60

Gln Ile Arg Glu Leu Arg Glu Lys Ser Glu Lys Phe Ala Phe Gln Ala
65 70 75 80

Glu Val Asn Arg Met Met Lys Leu Ile Ile Asn Ser Leu Tyr Lys Asn
85 90 95

Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu
100 105 110

Asp Lys Ile Arg Leu Ile Ser Leu Thr Asp Glu Asn Ala Leu Ser Gly
115 120 125

Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu
130 135 140

Leu His Val Thr Asp Thr Gly Val Gly Met Thr Arg Glu Glu Leu Val
145 150 155 160

Lys Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Ser Glu Phe Leu Asn
165 170 175

Lys Met Thr Glu Ala Gln Glu Asp Gly Gln Ser Thr Ser Glu Leu Ile
180 185 190

Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Phe Leu Val Ala Asp Lys
195 200 205

Val Ile Val Thr Ser Lys His Asn Asn Asp Thr Gln His Ile Trp Glu
210 215 220

Ser Asp Ser Asn Glu Phe Ser Val Ile Ala Asp Pro Arg Gly Asn Thr
225 230 235 240

Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu Glu Ala Ser
245 250 255

Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys Lys Tyr Ser
260 265 270

Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys Thr Glu Thr
275 280 285

Val Glu Glu Pro Met Glu Glu Glu Glu Ala Ala Lys Glu Glu Lys Glu
290 295 300

Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu Glu Lys Lys
305 310 315 320

Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp Glu Leu Met
325 330 335

Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu Val Glu Glu
340 345 350

Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu Ser Asp Asp
355 360 365

Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val Thr Phe Lys
370 375 380

Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu Phe Asp Glu
385 390 395 400

Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val Arg Arg Val
405 410 415

Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr Leu Asn Phe
420 425 430

Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn Val Ser Arg
435 440 445

Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg Lys Lys Leu
450 455 460

Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp Asp Lys Tyr
465 470 475 480

Asn Asp Thr Phe Trp Lys Glu Phe Gly Thr Asn Ile Lys Leu Gly Val
485 490 495

Ile Glu Asp His Ser Asn Arg Thr Arg Leu Ala Lys Leu Leu Arg Phe
500 505 510

Gln Ser Ser His His Pro Thr Asp Ile Thr Ser Leu Asp Gln Tyr Val
515 520 525

Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met Ala Gly Ser
530 535 540

Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg Leu Leu Lys
545 550 555 560

Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp Glu Tyr Cys
565 570 575

Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln Asn Val Ala
580 585 590

```
Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys Glu Ser Arg
        595                 600                 605

Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp Met Lys Asp
    610                 615                 620

Lys Ala Leu Lys Asp Lys Ile Glu Lys Ala Val Val Ser Gln Arg Leu
625                 630                 635                 640

Thr Glu Ser Pro Cys Ala Leu Val Ala Ser Gln Tyr Gly Trp Ser Gly
                645                 650                 655

Asn Met Glu Arg Ile Met Lys Ala Gln Ala Tyr Gln Thr Gly Lys Asp
            660                 665                 670

Ile Ser Thr Asn Tyr Tyr Ala Ser Gln Lys Lys Thr Phe Glu Ile Asn
        675                 680                 685

Pro Arg His Pro Leu Ile Arg Asp Met Leu Arg Arg Ile Lys Glu Asp
    690                 695                 700

Glu Asp Asp Lys Thr Val Leu Asp Leu Ala Val Val Leu Phe Glu Thr
705                 710                 715                 720

Ala Thr Leu Arg Ser Gly Tyr Leu Leu Pro Asp Thr Lys Ala Tyr Gly
                725                 730                 735

Asp Arg Ile Glu Arg Met Leu Arg Leu Ser Leu Asn Ile Asp Pro Asp
            740                 745                 750

Ala Lys Val Glu Glu Glu Pro Glu Glu Glu Pro Glu Glu Thr Ala Glu
        755                 760                 765

Asp Thr Thr Glu Asp Thr Glu Gln Asp Glu Asp Glu Glu Met Asp Val
    770                 775                 780

Gly Thr Asp Glu Glu Glu Glu Thr Ala Lys Glu Ser Thr Ala Glu Lys
785                 790                 795                 800

Asp Glu Leu
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<210> 79
<211> 4061
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (73)..(3717)
<223>

<400> 79

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ggccgcggca gc atg gtg gtg ccg gag aag gag cag agc tgg atc ccc aag     111
              Met Val Val Pro Glu Lys Glu Gln Ser Trp Ile Pro Lys
              1               5                   10

atc ttc aag aag aag acc tgc acg acg ttc ata gtt gac tcc aca gat       159
Ile Phe Lys Lys Lys Thr Cys Thr Thr Phe Ile Val Asp Ser Thr Asp
    15                  20                  25

ccg gga ggg acc ttg tgc cag tgt ggg cgc ccc cgg acc gcc cac ccc       207
Pro Gly Gly Thr Leu Cys Gln Cys Gly Arg Pro Arg Thr Ala His Pro
30                  35                  40                  45
```

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gca gtg gcc atg gag gat gcc ttc ggg gca gcc gtg gtg acc gtg tgg      255
Ala Val Ala Met Glu Asp Ala Phe Gly Ala Ala Val Val Thr Val Trp
                50                  55                  60

gac agc gat gca cac acc acg gag aag ccc acc gat gcc tac gga gag      303
Asp Ser Asp Ala His Thr Thr Glu Lys Pro Thr Asp Ala Tyr Gly Glu
            65                  70                  75

ctg gac ttc acg ggg gcc ggc cgc aag cac agc aat ttc ctc cgg ctc      351
Leu Asp Phe Thr Gly Ala Gly Arg Lys His Ser Asn Phe Leu Arg Leu
        80                  85                  90

tct gac cga acg gat cca gct gca gtt tat agt ctg gtc aca cgc aca      399
Ser Asp Arg Thr Asp Pro Ala Ala Val Tyr Ser Leu Val Thr Arg Thr
    95                  100                 105

tgg ggc ttc cgt gcc ccg aac ctg gtg gtg tca gtg ctg ggg gga tcg      447
Trp Gly Phe Arg Ala Pro Asn Leu Val Val Ser Val Leu Gly Gly Ser
110                 115                 120                 125

ggg ggc ccc gtc ctc cag acc tgg ctg cag gac ctg ctg cgt cgt ggg      495
Gly Gly Pro Val Leu Gln Thr Trp Leu Gln Asp Leu Leu Arg Arg Gly
                130                 135                 140

ctg gtg cgg gct gcc cag agc aca gga gcc tgg att gtc act ggg ggt      543
Leu Val Arg Ala Ala Gln Ser Thr Gly Ala Trp Ile Val Thr Gly Gly
            145                 150                 155

ctg cac acg ggc atc ggc cgg cat gtt ggt gtg gct gta cgg gac cat      591
Leu His Thr Gly Ile Gly Arg His Val Gly Val Ala Val Arg Asp His
        160                 165                 170

cag atg gcc agc act ggg ggc acc aag gtg gtg gcc atg ggt gtg gcc      639
Gln Met Ala Ser Thr Gly Gly Thr Lys Val Val Ala Met Gly Val Ala
    175                 180                 185

ccc tgg ggt gtg gtc cgg aat aga gac acc ctc atc aac ccc aag ggc      687
Pro Trp Gly Val Val Arg Asn Arg Asp Thr Leu Ile Asn Pro Lys Gly
190                 195                 200                 205

tcg ttc cct gcg agg tac cgg tgg cgc ggt gac ccg gag gac ggg gtc      735
Ser Phe Pro Ala Arg Tyr Arg Trp Arg Gly Asp Pro Glu Asp Gly Val
                210                 215                 220

cag ttt ccc ctg gac tac aac tac tcg gcc ttc ttc ctg gtg gac gac      783
Gln Phe Pro Leu Asp Tyr Asn Tyr Ser Ala Phe Phe Leu Val Asp Asp
            225                 230                 235

ggc aca cac ggc tgc ctg ggg ggc gag aac cgc ttc cgc ttg cgc ctg      831
Gly Thr His Gly Cys Leu Gly Gly Glu Asn Arg Phe Arg Leu Arg Leu
        240                 245                 250

gag tcc tac atc tca cag cag aag acg ggc gtg gga ggg act gga att      879
Glu Ser Tyr Ile Ser Gln Gln Lys Thr Gly Val Gly Gly Thr Gly Ile
    255                 260                 265

gac atc cct gtc ctg ctc ctc ctg att gat ggt gat gag aag atg ttg      927
Asp Ile Pro Val Leu Leu Leu Leu Ile Asp Gly Asp Glu Lys Met Leu
270                 275                 280                 285

acg cga ata gag aac gcc acc cag gct cag ctc cca tgt ctc ctc gtg      975
Thr Arg Ile Glu Asn Ala Thr Gln Ala Gln Leu Pro Cys Leu Leu Val
                290                 295                 300

gct ggc tca ggg gga gct gcg gac tgc ctg gcg gag acc ctg gaa gac     1023
Ala Gly Ser Gly Gly Ala Ala Asp Cys Leu Ala Glu Thr Leu Glu Asp
            305                 310                 315

act ctg gcc cca ggg agt ggg gga gcc agg caa ggc gaa gcc cga gat     1071
Thr Leu Ala Pro Gly Ser Gly Gly Ala Arg Gln Gly Glu Ala Arg Asp
        320                 325                 330

cga atc agg cgt ttc ttt ccc aaa ggg gac ctt gag gtc ctg cag gcc     1119
Arg Ile Arg Arg Phe Phe Pro Lys Gly Asp Leu Glu Val Leu Gln Ala
    335                 340                 345

cag gtg gag agg att atg acc cgg aag gag ctc ctg aca gtc tat tct     1167
Gln Val Glu Arg Ile Met Thr Arg Lys Glu Leu Leu Thr Val Tyr Ser
350                 355                 360                 365
```

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tct gag gat ggg tct gag gaa ttc gag acc ata gtt ttg aag gcc ctt      1215
Ser Glu Asp Gly Ser Glu Glu Phe Glu Thr Ile Val Leu Lys Ala Leu
                370                 375                 380

gtg aag gcc tgt ggg agc tcg gag gcc tca gcc tac ctg gat gag ctg      1263
Val Lys Ala Cys Gly Ser Ser Glu Ala Ser Ala Tyr Leu Asp Glu Leu
            385                 390                 395

cgt ttg gct gtg gct tgg aac cgc gtg gac att gcc cag agt gaa ctc      1311
Arg Leu Ala Val Ala Trp Asn Arg Val Asp Ile Ala Gln Ser Glu Leu
        400                 405                 410

ttt cgg ggg gac atc caa tgg cgg tcc ttc cat ctc gaa gct tcc ctc      1359
Phe Arg Gly Asp Ile Gln Trp Arg Ser Phe His Leu Glu Ala Ser Leu
    415                 420                 425

atg gac gcc ctg ctg aat gac cgg cct gag ttc gtg cgc ttg ctc att      1407
Met Asp Ala Leu Leu Asn Asp Arg Pro Glu Phe Val Arg Leu Leu Ile
430                 435                 440                 445

tcc cac ggc ctc agc ctg ggc cac ttc ctg acc ccg atg cgc ctg gcc      1455
Ser His Gly Leu Ser Leu Gly His Phe Leu Thr Pro Met Arg Leu Ala
                450                 455                 460

caa ctc tac agc gcg gcg ccc tcc aac tcg ctc atc cgc aac ctt ttg      1503
Gln Leu Tyr Ser Ala Ala Pro Ser Asn Ser Leu Ile Arg Asn Leu Leu
            465                 470                 475

gac cag gcg tcc cac agc gca ggc acc aaa gcc cca gcc cta aaa ggg      1551
Asp Gln Ala Ser His Ser Ala Gly Thr Lys Ala Pro Ala Leu Lys Gly
        480                 485                 490

gga gct gcg gag ctc cgg ccc cct gac gtg ggg cat gtg ctg agg atg      1599
Gly Ala Ala Glu Leu Arg Pro Pro Asp Val Gly His Val Leu Arg Met
    495                 500                 505

ctg ctg ggg aag atg tgc gcg ccg agg tac ccc tcc ggg ggc gcc tgg      1647
Leu Leu Gly Lys Met Cys Ala Pro Arg Tyr Pro Ser Gly Gly Ala Trp
510                 515                 520                 525

gac cct cac cca ggc cag ggc ttc ggg gag agc atg tat ctg ctc tcg      1695
Asp Pro His Pro Gly Gln Gly Phe Gly Glu Ser Met Tyr Leu Leu Ser
                530                 535                 540

gac aag gcc acc tcg ccg ctc tcg ctg gat gct ggc ctc ggg cag gcc      1743
Asp Lys Ala Thr Ser Pro Leu Ser Leu Asp Ala Gly Leu Gly Gln Ala
            545                 550                 555

ccc tgg agc gac ctg ctt ctt tgg gca ctg ttg ctg aac agg gca cag      1791
Pro Trp Ser Asp Leu Leu Leu Trp Ala Leu Leu Leu Asn Arg Ala Gln
        560                 565                 570

atg gcc atg tac ttc tgg gag atg ggt tcc aat gca gtt tcc tca gct      1839
Met Ala Met Tyr Phe Trp Glu Met Gly Ser Asn Ala Val Ser Ser Ala
    575                 580                 585

ctt ggg gcc tgt ttg ctg ctc cgg gtg atg gca cgc ctg gag cct gac      1887
Leu Gly Ala Cys Leu Leu Leu Arg Val Met Ala Arg Leu Glu Pro Asp
590                 595                 600                 605

gct gag gag gca gca cgg agg aaa gac ctg gcg ttc aag ttt gag ggg      1935
Ala Glu Glu Ala Ala Arg Arg Lys Asp Leu Ala Phe Lys Phe Glu Gly
                610                 615                 620

atg ggc gtt gac ctc ttt ggc gag tgc tat cgc agc agt gag gtg agg      1983
Met Gly Val Asp Leu Phe Gly Glu Cys Tyr Arg Ser Ser Glu Val Arg
            625                 630                 635

gct gcc cgc ctc ctc ctc cgt cgc tgc ccg ctc tgg ggg gat gcc act      2031
Ala Ala Arg Leu Leu Leu Arg Arg Cys Pro Leu Trp Gly Asp Ala Thr
        640                 645                 650

tgc ctc cag ctg gcc atg caa gct gac gcc cgt gcc ttc ttt gcc cag      2079
Cys Leu Gln Leu Ala Met Gln Ala Asp Ala Arg Ala Phe Phe Ala Gln
    655                 660                 665

gat ggg gta cag tct ctg ctg aca cag aag tgg tgg gga gat atg gcc      2127
Asp Gly Val Gln Ser Leu Leu Thr Gln Lys Trp Trp Gly Asp Met Ala
670                 675                 680                 685
```

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agc act aca ccc atc tgg gcc ctg gtt ctc gcc ttc ttt tgc cct cca      2175
Ser Thr Thr Pro Ile Trp Ala Leu Val Leu Ala Phe Phe Cys Pro Pro
                690                 695                 700

ctc atc tac acc cgc ctc atc acc ttc agg aaa tca gaa gag gag ccc      2223
Leu Ile Tyr Thr Arg Leu Ile Thr Phe Arg Lys Ser Glu Glu Glu Pro
            705                 710                 715

aca cgg gag gag cta gag ttt gac atg gat agt gtc att aat ggg gaa      2271
Thr Arg Glu Glu Leu Glu Phe Asp Met Asp Ser Val Ile Asn Gly Glu
        720                 725                 730

ggg cct gtc ggg acg gcg gac cca gcc gag aag acg ccg ctg ggg gtc      2319
Gly Pro Val Gly Thr Ala Asp Pro Ala Glu Lys Thr Pro Leu Gly Val
    735                 740                 745

ccg cgc cag tcg ggc cgt ccg ggt tgc tgc ggg ggc cgc tgc ggg ggg      2367
Pro Arg Gln Ser Gly Arg Pro Gly Cys Cys Gly Gly Arg Cys Gly Gly
750                 755                 760                 765

cgc cgg tgc cta cgc cgc tgg ttc cac ttc tgg ggc gcg ccg gtg acc      2415
Arg Arg Cys Leu Arg Arg Trp Phe His Phe Trp Gly Ala Pro Val Thr
                770                 775                 780

atc ttc atg ggc aac gtg gtc agc tac ctg ctg ttc ctg ctg ctt ttc      2463
Ile Phe Met Gly Asn Val Val Ser Tyr Leu Leu Phe Leu Leu Leu Phe
            785                 790                 795

tcg cgg gtg ctg ctc gtg gat ttc cag ccg gcg ccg ccc ggc tcc ctg      2511
Ser Arg Val Leu Leu Val Asp Phe Gln Pro Ala Pro Pro Gly Ser Leu
        800                 805                 810

gag ctg ctg ctc tat ttc tgg gct ttc acg ctg ctg tgc gag gaa ctg      2559
Glu Leu Leu Leu Tyr Phe Trp Ala Phe Thr Leu Leu Cys Glu Glu Leu
    815                 820                 825

cgc cag ggc ctg agc gga ggc ggg ggc agc ctc gcc agc ggg ggc ccc      2607
Arg Gln Gly Leu Ser Gly Gly Gly Gly Ser Leu Ala Ser Gly Gly Pro
830                 835                 840                 845

ggg cct ggc cat gcc tca ctg agc cag cgc ctg cgc ctc tac ctc gcc      2655
Gly Pro Gly His Ala Ser Leu Ser Gln Arg Leu Arg Leu Tyr Leu Ala
                850                 855                 860

gac agc tgg aac cag tgc gac cta gtg gct ctc acc tgc ttc ctc ctg      2703
Asp Ser Trp Asn Gln Cys Asp Leu Val Ala Leu Thr Cys Phe Leu Leu
            865                 870                 875

ggc gtg ggc tgc cgg ctg acc ccg ggt ttg tac cac ctg ggc cgc act      2751
Gly Val Gly Cys Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr
        880                 885                 890

gtc ctc tgc atc gac ttc atg gtt ttc acg gtg cgg ctg ctt cac atc      2799
Val Leu Cys Ile Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile
    895                 900                 905

ttc acg gtc aac aaa cag ctg ggg ccc aag atc gtc atc gtg agc aag      2847
Phe Thr Val Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys
910                 915                 920                 925

atg atg aag gac gtg ttc ttc ttc ctc ttc ttc ctc ggc gtg tgg ctg      2895
Met Met Lys Asp Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu
                930                 935                 940

gta gcc tat ggc gtg gcc acg gag ggg ctc ctg agg cca cgg gac agt      2943
Val Ala Tyr Gly Val Ala Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser
            945                 950                 955

gac ttc cca agt atc ctg cgc cgc gtc ttc tac cgt ccc tac ctg cag      2991
Asp Phe Pro Ser Ile Leu Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln
        960                 965                 970

atc ttc ggg cag att ccc cag gag gac atg gac gtg gcc ctc atg gag      3039
Ile Phe Gly Gln Ile Pro Gln Glu Asp Met Asp Val Ala Leu Met Glu
    975                 980                 985

cac agc aac tgc tcg tcg gag ccc ggc ttc tgg  gca cac cct cct ggg      3087
His Ser Asn Cys Ser Ser Glu Pro Gly Phe Trp  Ala His Pro Pro Gly
990                 995                1000                1005
```

```
gcc cag gcg ggc acc  tgc gtc tcc cag tat  gcc aac tgg ctg gtg        3132
Ala Gln Ala Gly Thr  Cys Val Ser Gln Tyr  Ala Asn Trp Leu Val
                1010                1015                1020

gtg ctg ctc ctc gtc  atc ttc ctg ctc gtg  gcc aac atc ctg ctg        3177
Val Leu Leu Leu Val  Ile Phe Leu Leu Val  Ala Asn Ile Leu Leu
                1025                1030                1035

gtc aac ttg ctc att  gcc atg ttc agt tac  aca ttc ggc aaa gta        3222
Val Asn Leu Leu Ile  Ala Met Phe Ser Tyr  Thr Phe Gly Lys Val
                1040                1045                1050

cag ggc aac agc gat  ctc tac tgg aag gcg  cag cgt tac cgc ctc        3267
Gln Gly Asn Ser Asp  Leu Tyr Trp Lys Ala  Gln Arg Tyr Arg Leu
                1055                1060                1065

atc cgg gaa ttc cac  tct cgg ccc gcg ctg  gcc ccg ccc ttt atc        3312
Ile Arg Glu Phe His  Ser Arg Pro Ala Leu  Ala Pro Pro Phe Ile
                1070                1075                1080

gtc atc tcc cac ttg  cgc ctc ctg ctc agg  caa ttg tgc agg cga        3357
Val Ile Ser His Leu  Arg Leu Leu Leu Arg  Gln Leu Cys Arg Arg
                1085                1090                1095

ccc cgg agc ccc cag  ccg tcc tcc ccg gcc  ctc gag cat ttc cgg        3402
Pro Arg Ser Pro Gln  Pro Ser Ser Pro Ala  Leu Glu His Phe Arg
                1100                1105                1110

gtt tac ctt tct aag  gaa gcc gag cgg aag  ctg cta acg tgg gaa        3447
Val Tyr Leu Ser Lys  Glu Ala Glu Arg Lys  Leu Leu Thr Trp Glu
                1115                1120                1125

tcg gtg cat aag gag  aac ttt ctg ctg gca  cgc gct agg gac aag        3492
Ser Val His Lys Glu  Asn Phe Leu Leu Ala  Arg Ala Arg Asp Lys
                1130                1135                1140

cgg gag agc gac tcc  gag cgt ctg aag cgc  acg tcc cag aag gtg        3537
Arg Glu Ser Asp Ser  Glu Arg Leu Lys Arg  Thr Ser Gln Lys Val
                1145                1150                1155

gac ttg gca ctg aaa  cag ctg gga cac atc  cgc gag tac gaa cag        3582
Asp Leu Ala Leu Lys  Gln Leu Gly His Ile  Arg Glu Tyr Glu Gln
                1160                1165                1170

cgc ctg aaa gtg ctg  gag cgg gag gtc cag  cag tgt agc cgc gtc        3627
Arg Leu Lys Val Leu  Glu Arg Glu Val Gln  Gln Cys Ser Arg Val
                1175                1180                1185

ctg ggg tgg gtg gcc  gag gcc ctg agc cgc  tct gcc ttg ctg ccc        3672
Leu Gly Trp Val Ala  Glu Ala Leu Ser Arg  Ser Ala Leu Leu Pro
                1190                1195                1200

cca ggt ggg ccg cca  ccc cct gac ctg cct  ggg tcc aaa gac tga        3717
Pro Gly Gly Pro Pro  Pro Pro Asp Leu Pro  Gly Ser Lys Asp
                1205                1210

gccctgctgg cggacttcaa ggagaagccc ccacagggga ttttgctcct agagtaaggc   3777

tcatctgggc ctcggccccc gcacctggtg gccttgtcct tgaggtgagc cccatgtcca   3837

tctgggccac tgtcaggacc acctttggga gtgtcatcct tacaaaccac agcatgcccg   3897

gctcctccca gaaccagtcc cagcctggga ggatcaaggc ctggatcccg ggccgttatc   3957

catctggagg ctgcagggtc cttggggtaa cagggaccac agacccctca ccactcacag   4017

attcctcaca ctggggaaat aaagccattt cagaggaaaa aaaa                    4061
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<210> 80
<211> 1214
<212> PRT
<213> Homo sapiens

<400> 80

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1               5                  10                  15
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Lys Lys Thr Cys Thr Thr Phe Ile Val Asp Ser Thr Asp Pro Gly Gly
20 25 30

Thr Leu Cys Gln Cys Gly Arg Pro Arg Thr Ala His Pro Ala Val Ala
35 40 45

Met Glu Asp Ala Phe Gly Ala Ala Val Val Thr Val Trp Asp Ser Asp
50 55 60

Ala His Thr Thr Glu Lys Pro Thr Asp Ala Tyr Gly Glu Leu Asp Phe
65 70 75 80

Thr Gly Ala Gly Arg Lys His Ser Asn Phe Leu Arg Leu Ser Asp Arg
85 90 95

Thr Asp Pro Ala Ala Val Tyr Ser Leu Val Thr Arg Thr Trp Gly Phe
100 105 110

Arg Ala Pro Asn Leu Val Val Ser Val Leu Gly Gly Ser Gly Gly Pro
115 120 125

Val Leu Gln Thr Trp Leu Gln Asp Leu Leu Arg Arg Gly Leu Val Arg
130 135 140

Ala Ala Gln Ser Thr Gly Ala Trp Ile Val Thr Gly Gly Leu His Thr
145 150 155 160

Gly Ile Gly Arg His Val Gly Val Ala Val Arg Asp His Gln Met Ala
165 170 175

Ser Thr Gly Gly Thr Lys Val Val Ala Met Gly Val Ala Pro Trp Gly
180 185 190

Val Val Arg Asn Arg Asp Thr Leu Ile Asn Pro Lys Gly Ser Phe Pro
195 200 205

Ala Arg Tyr Arg Trp Arg Gly Asp Pro Glu Asp Gly Val Gln Phe Pro
210 215 220

Leu Asp Tyr Asn Tyr Ser Ala Phe Phe Leu Val Asp Asp Gly Thr His
225 230 235 240

Gly Cys Leu Gly Gly Glu Asn Arg Phe Arg Leu Arg Leu Glu Ser Tyr
245 250 255

Ile Ser Gln Gln Lys Thr Gly Val Gly Gly Thr Gly Ile Asp Ile Pro
260 265 270

Val Leu Leu Leu Leu Ile Asp Gly Asp Glu Lys Met Leu Thr Arg Ile
275 280 285

Glu Asn Ala Thr Gln Ala Gln Leu Pro Cys Leu Leu Val Ala Gly Ser
290 295 300

Gly Gly Ala Ala Asp Cys Leu Ala Glu Thr Leu Glu Asp Thr Leu Ala
305 310 315 320

Pro Gly Ser Gly Gly Ala Arg Gln Gly Glu Ala Arg Asp Arg Ile Arg
325 330 335

Arg Phe Phe Pro Lys Gly Asp Leu Glu Val Leu Gln Ala Gln Val Glu
340 345 350

Arg Ile Met Thr Arg Lys Glu Leu Leu Thr Val Tyr Ser Ser Glu Asp
355 360 365

Gly Ser Glu Glu Phe Glu Thr Ile Val Leu Lys Ala Leu Val Lys Ala
370 375 380

Cys Gly Ser Ser Glu Ala Ser Ala Tyr Leu Asp Glu Leu Arg Leu Ala
385 390 395 400

Val Ala Trp Asn Arg Val Asp Ile Ala Gln Ser Glu Leu Phe Arg Gly
405 410 415

Asp Ile Gln Trp Arg Ser Phe His Leu Glu Ala Ser Leu Met Asp Ala
420 425 430

Leu Leu Asn Asp Arg Pro Glu Phe Val Arg Leu Leu Ile Ser His Gly
435 440 445

Leu Ser Leu Gly His Phe Leu Thr Pro Met Arg Leu Ala Gln Leu Tyr
450 455 460

Ser Ala Ala Pro Ser Asn Ser Leu Ile Arg Asn Leu Leu Asp Gln Ala
465 470 475 480

Ser His Ser Ala Gly Thr Lys Ala Pro Ala Leu Lys Gly Gly Ala Ala
485 490 495

Glu Leu Arg Pro Pro Asp Val Gly His Val Leu Arg Met Leu Leu Gly
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Lys Met Cys Ala Pro Arg Tyr Pro Ser Gly Gly Ala Trp Asp Pro His
515 520 525

Pro Gly Gln Gly Phe Gly Glu Ser Met Tyr Leu Leu Ser Asp Lys Ala
530 535 540

Thr Ser Pro Leu Ser Leu Asp Ala Gly Leu Gly Gln Ala Pro Trp Ser
545 550 555 560

Asp Leu Leu Leu Trp Ala Leu Leu Leu Asn Arg Ala Gln Met Ala Met
565 570 575

Tyr Phe Trp Glu Met Gly Ser Asn Ala Val Ser Ser Ala Leu Gly Ala
580 585 590

Cys Leu Leu Leu Arg Val Met Ala Arg Leu Glu Pro Asp Ala Glu Glu
595 600 605

Ala Ala Arg Arg Lys Asp Leu Ala Phe Lys Phe Glu Gly Met Gly Val
610 615 620

Asp Leu Phe Gly Glu Cys Tyr Arg Ser Ser Glu Val Arg Ala Ala Arg
625 630 635 640

Leu Leu Leu Arg Arg Cys Pro Leu Trp Gly Asp Ala Thr Cys Leu Gln
645 650 655

Leu Ala Met Gln Ala Asp Ala Arg Ala Phe Phe Ala Gln Asp Gly Val
660 665 670

Gln Ser Leu Leu Thr Gln Lys Trp Trp Gly Asp Met Ala Ser Thr Thr
675 680 685

Pro Ile Trp Ala Leu Val Leu Ala Phe Phe Cys Pro Pro Leu Ile Tyr
690 695 700

Thr Arg Leu Ile Thr Phe Arg Lys Ser Glu Glu Glu Pro Thr Arg Glu
705 710 715 720

Glu Leu Glu Phe Asp Met Asp Ser Val Ile Asn Gly Glu Gly Pro Val
725 730 735

Gly Thr Ala Asp Pro Ala Glu Lys Thr Pro Leu Gly Val Pro Arg Gln
740 745 750

Ser Gly Arg Pro Gly Cys Cys Gly Gly Arg Cys Gly Gly Arg Arg Cys
755 760 765

Leu Arg Arg Trp Phe His Phe Trp Gly Ala Pro Val Thr Ile Phe Met
770 775 780

Gly Asn Val Val Ser Tyr Leu Leu Phe Leu Leu Leu Phe Ser Arg Val
785 790 795 800

Leu Leu Val Asp Phe Gln Pro Ala Pro Pro Gly Ser Leu Glu Leu Leu
805 810 815

Leu Tyr Phe Trp Ala Phe Thr Leu Leu Cys Glu Glu Leu Arg Gln Gly
820 825 830

Leu Ser Gly Gly Gly Gly Ser Leu Ala Ser Gly Gly Pro Gly Pro Gly
835 840 845

His Ala Ser Leu Ser Gln Arg Leu Arg Leu Tyr Leu Ala Asp Ser Trp
850 855 860

Asn Gln Cys Asp Leu Val Ala Leu Thr Cys Phe Leu Leu Gly Val Gly
865 870 875 880

Cys Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr Val Leu Cys
885 890 895

Ile Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val
900 905 910

Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys
915 920 925

Asp Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr
930 935 940

Gly Val Ala Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro
945 950 955 960

Ser Ile Leu Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly
965 970 975

Gln Ile Pro Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn
980 985 990

Cys Ser Ser Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala
995 1000 1005

Gly Thr Cys Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu
1010 1015 1020

Leu Val Ile Phe Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu
1025 1030 1035

Leu Ile Ala Met Phe Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn
1040 1045 1050

Ser Asp Leu Tyr Trp Lys Ala Gln Arg Tyr Arg Leu Ile Arg Glu
1055 1060 1065

Phe His Ser Arg Pro Ala Leu Ala Pro Pro Phe Ile Val Ile Ser
1070 1075 1080

His Leu Arg Leu Leu Leu Arg Gln Leu Cys Arg Arg Pro Arg Ser
1085 1090 1095

Pro Gln Pro Ser Ser Pro Ala Leu Glu His Phe Arg Val Tyr Leu
1100 1105 1110

Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr Trp Glu Ser Val His
1115 1120 1125

Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp Lys Arg Glu Ser
1130 1135 1140

Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val Asp Leu Ala
1145 1150 1155

Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg Leu Lys
1160 1165 1170

Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly Trp
1175 1180 1185

Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly
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Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp
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